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Conflicting clinical observations on the effect of peripheral circulatory changes in the glomus tumor have been reported. The characteristic bluish or bluish red color of the nodule during the painful crisis is due to the congestion in the blood spaces. Wood¹¹ noted in several of his 10 clinical cases that "during the painful crisis there was an increase in size of the tubercle and purplish or bluish discoloration of the skin at the same time." Likewise Mason and Weil¹² found that "compression of the tumor, or in other words emptying the blood vessels was immediately followed by the disappearance of the feeling of intense pain. Refilling of the vessels, indicated by the reappearance of the bluish color of the tumor, brought back again the painful sensation." Greig,¹³ Lortat-Jacob and Brosse,¹⁴ and Bonnet¹⁵ also noted in some of their cases that cold relieved the painful crisis and warmth aggravated it. Conversely, Hall¹⁶ described a typical clinical case in which the pain was "caused by and aggravated by cold, and relieved by warmth." Likewise, Masson,⁴ Ianichewski and Lebel¹⁷ and Raisman and Mayer¹⁸ reported similar observations on the effect of heat and cold.

Paulian and his co-workers¹⁹ described a case of subungual tumor of the finger in which they observed during the attacks of pain an increase in temperature of from 0.5 to 2 C. on the affected side as compared to the normal side. After local excision of the tumor this

8. Keasbey, Louisa E.: Tumors of Glomus, *Internat. J. Med. & Surg.* **46**:431-432 (Sept.) 1933.

9. Adair, F. E.: Glomus Tumor: A Clinical Study with a Report of Ten Cases, *Am. J. Surg.* **25**:1-6 (July) 1934.

10. Burman, M. S., and Gold, A. M.: Glomus Tumor: Brief Clinical Study of Glomus Angio-Myo-Neurome Artériel of Barré and Masson, *New York State J. Med.* **35**:618-620 (June 15) 1935.

11. Wood, W.: On Painful Subcutaneous Tubercles, *Edinburgh M. & S. J.* **8**:283-291, 1812.

12. Mason, Michael, and Weil, Arthur: Tumor of a Subcutaneous Glomus, *Surg., Gynec. & Obst.* **58**:807-816 (May) 1934.

13. Greig, D. M.: Subcutaneous Glomus Tumors: Painful Subcutaneous Nodule, *Edinburgh M. J.* **35**:565-582 (Oct.) 1928.

14. Lortat-Jacob, L., and Brosse, T.: Tumeur sous-unguéale violacée, *Bull. Soc. franç. de dermat. et syph.* **35**:305-309 (April) 1928.

15. Bonnet, M. P.: Tumeur sous-unguéale douloureuse (glomus), *Lyon chir.* **24**:718-721, 1927.

16. Hall, M.: Case of Painful Subcutaneous Tubercle, *Edinburgh M. & S. J.* **11**:466, 1815.

17. Ianichewski, A., and Lebel, M.: Une variété de névralgie; la sympathalgie due à une tumeur glomique, *Presse méd.* **36**:116-118 (Jan. 28) 1928.

18. Raisman, Victor, and Mayer, Leo: Tumor of the Neuromyo-Arterial Glomus, *Arch. Surg.* **30**:911-929 (June) 1935.

19. Paulian, D.; Stefan-Popescu and Marinesco-Slatina, D.: Subungual Glomus Tumor Causing Hemihyperthermia: Complete Cure After Surgical Removal, *Ann. d'anat. path.* **10**:271-276 (March) 1933.

REPORT OF A CASE

E. M., aged 69, of Irish birth, a machinist, was examined on Feb. 5, 1935. For more than one year he had constant pain in the calf of the right leg (rest pains). The pain became especially severe after he walked two or three blocks, and he had to rest a few minutes before continuing (intermittent claudication). Pulsation was absent in both the dorsalis pedis and the posterior tibial artery but was present in the popliteal artery. A roentgenogram revealed marked sclerosis of the arteries of the right leg and foot. The foot was definitely cold to touch, and the patient stated that the coldness had troubled him for years. There was no ulceration or dependent discoloration. The left foot and leg had given no trouble, and all arterial pulsations were moderately palpable.

On March 7, after sixteen hours of treatment with positive and negative pressure, the patient reported complete relief from intermittent claudication and rest pains, which enabled him to return to physical labor. On March 18 thermocouple temperature readings after stabilization at 23 C. revealed almost normal circulation in the right foot. The patient's condition continued to be satisfactory until April 30, when he reported that he felt fine except for the excruciating pains in the right first toe. On examination a firm very tender, bluish nodule the size of a pea was found protruding from beneath the tip of the toe-nail (fig. 1). This was

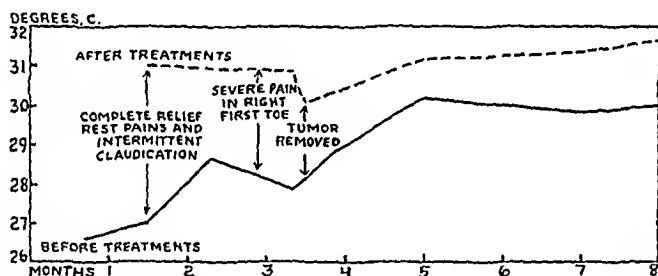


Fig. 2.—Chart showing thermocouple temperature readings in centigrade of the right first toe before (solid line) and after (interrupted line) one hour treatments with alternating positive and negative pressure over a period of eight months. Note the drop in temperature as the excruciating pains develop in the right first toe. After excision of the tumor the rapid improvement in temperature readings was maintained.

so tender that palpation was almost impossible. A roentgenogram of the toe showed no osseous changes or exostoses. The treatments with positive and negative pressure aggravated the excruciating pains. Because a roentgenogram failed to show a subungual exostosis, a diagnosis of subungual glomus tumor was made. On May 21, the tumor was removed. The wound healed rapidly, and the patient was free from all symptoms. No further treatments for the peripheral circulatory disease were given until August 22 when the patient complained of the return of the intermittent claudication. Prompt relief was obtained by treatments with alternating positive and negative pressure. By September 12, he was again able to walk rapidly for more than a mile (1.6 Km.) without distress or resting. He also stated that his legs perspired, an occurrence which he had not noticed for years. Without further treatments he has had occasional periodic return of intermittent claudication. However, the right first toe has caused no further trouble (November 20), and he has no rest pains. The stabilized peripheral tem-

perature has remained within normal limits, and the patient recently walked 7 miles (11.2 Km.) without distress or resting.

Comment.—The coldness of the extremity to palpation, the intermittent claudication and the rest pains indicated deficiency in the peripheral circulation. A

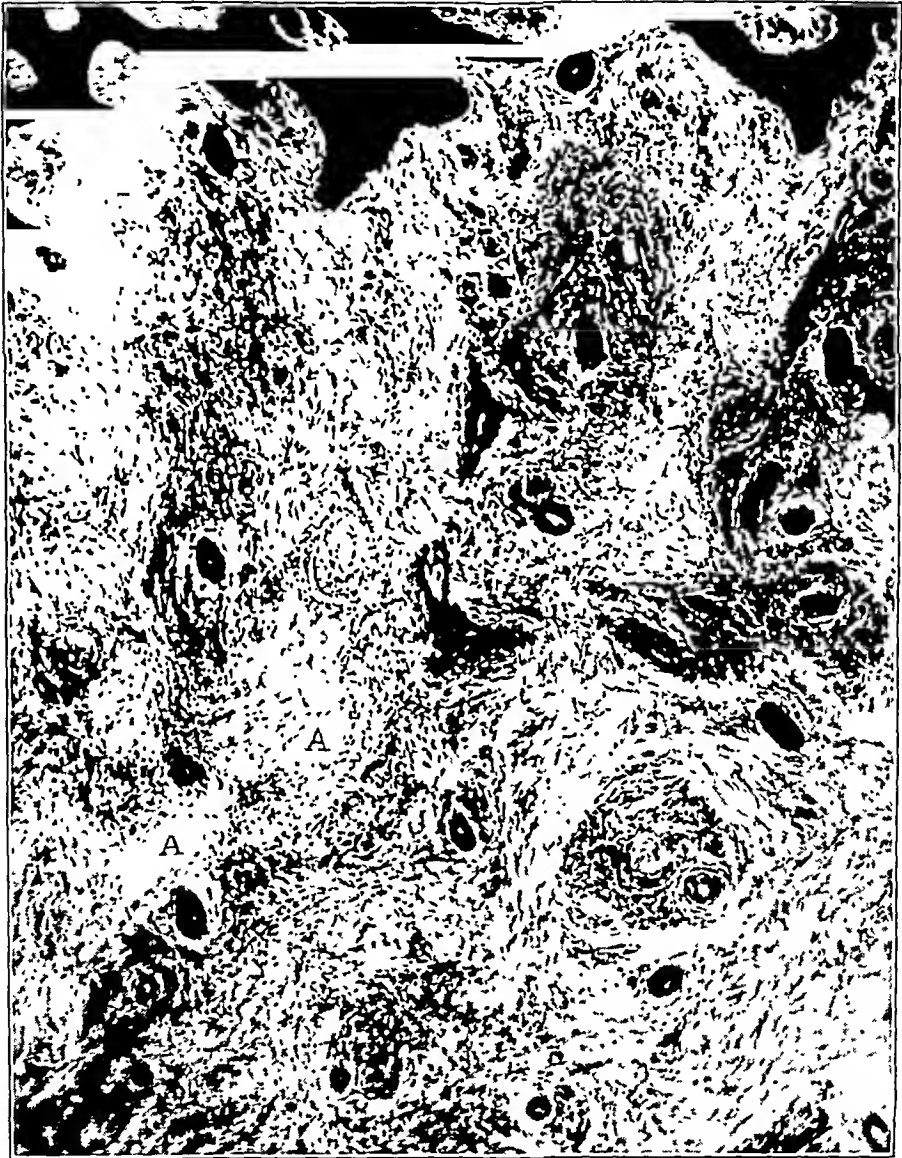


Fig. 3.—Low power photomicrograph of a section of a glomus tumor. The dark cellular structures are hyperplastic glomus units, with intervening loose collagenous connective tissue. A indicates the empty venous spaces.

roentgenogram of the right leg and foot revealed marked sclerosis of the arteries. As the circulation was improved by treatments with positive and negative pressure, the foregoing symptoms and clinical findings disappeared. With the return of

normal peripheral temperature, the circulation was sufficient to engorge the capillaries in the glomus tumor of the right first toe, with resulting excruciating pain. A drop in the peripheral temperature was then noticed (fig. 2). This was probably due to an arteriospasm caused by the painful tumor. Excision of the tumor brought relief from pain and almost normal circulation. An improvement was found not only in the temperature readings but to a slight degree in the oscillometric readings.

Pathologic Picture.—Grossly, the small, firm, elongated, fleshy tumor measured about 1 by 0.5 cm. and 0.6 cm. in depth. The epidermal covering was firm and tough, while the underlying tissue was soft and spongy. There was no capsule or line of separation between the nodule and the normal tissue.

Sections were prepared and stained with Mallory's eosin and methylene blue, hematoxylin and eosin, Mallory's phosphotungstic acid and hematoxylin and by the methods of Van Gieson and Davenport and Foote's modification of Bielschowsky's method.

Microscopic examination under low power magnification (fig. 3) revealed a thickened layer of normal epidermis. In the corium irregularly distributed clusters of dense basophilic cellular structures extended throughout the section. These areas were separated by loose collagenous connective tissue, within which thin-walled empty endothelium-lined spaces appeared. Within the dense basophilic cluster of cells there was a centrally located thick-walled vessel with a small lumen.

Under high power magnification characteristic glomus structures were seen (fig. 4). Each cluster of basophilic cells contained from four to six centrally located vessels resembling coil glands which were lined with several layers of epithelioid or glomus cells. Some of these cells with oval or round cell nuclei contained well defined nucleoli. The cytoplasm was clear and faintly staining. A few spindle-shaped forms were present. No mitotic figures were seen. The lumens of these vessels were empty, irregularly shaped and usually eccentrically located. Around the circular groups of glomus cells was a well defined layer of flat muscle cells. These units were described as the Sucquet-Hoyer canals²¹ of the S-shaped arteriovenous anastomoses. Collecting veins were seen as slitlike spaces around these structures. They were easily mistaken for artefacts but could be clearly demonstrated to be lined with a thin layer of flat endothelium. Vessels of a third type seen in this tumor were the preglomeric arterioles with large lumens. These were the tortuous vessels with a single layer of endothelium of flat elongated cells with oval nuclei. The elastic lamina was retained in these vessels, and they were found therefore filled with red blood corpuscles.

A satisfactory preparation by the silver staining method of Davenport was not obtained. However, with Foote's modification of the Bielschowsky method numerous argentophilic fibers were seen extending between the epithelioid or the glomus cells toward the lumen of the Sucquet-Hoyer canals.

COMMENT

A neuromyo-arterial glomus tumor is a rare form of blood vessel neoplasm. Geschickter and Keasbey,²² in reporting on a series of 570

21. Picard, Hugo: Ueber seltene Tumorem am Nagelbett, *Zentralbl. f. Chir.* **58**:2133-2135, 1931. Masson.⁴

22. Geschickter, Charles F., and Keasbey, Louisa E.: Tumors of Blood Vessels, *Am. J. Cancer* **23**:568-591 (March) 1935.

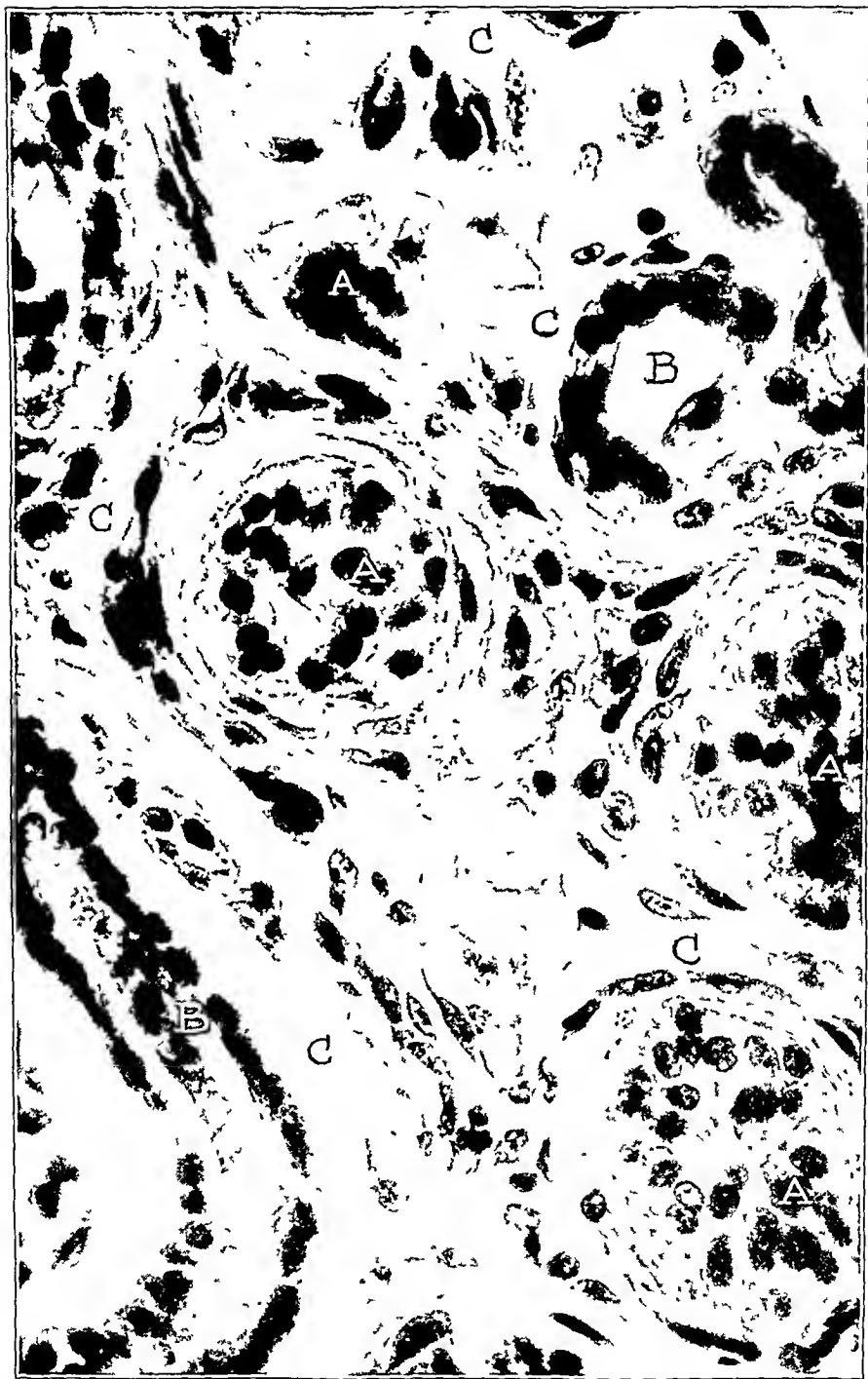


Fig 4—High power photomicrograph of a section of a glomus tumor showing four Sucquet-Hoyer canals (A) with small empty lumen (note the epithelioid or glomus cells of several layers thickness); preglomerular arterioles filled with red blood cells (B) and flat endothelial-lined collecting veins (C)

clinical and pathologic tumors of blood vessels from the Johns Hopkins Hospital, included 10 glomus tumors; 6 of the tumors were located on the hand or fingers, 2 on the leg or thigh, 2 on the forearm and none on the toes. More recently, Lewis and Geschickter²³ collected from the laboratory of surgical pathology of the Johns Hopkins Hospital reports of 17 cases, in 4 of which the tumor was subungual. As the terminology suggested by Masson indicates, nervous and muscular structures and blood vessels predominate in the tumor. Nerve fibers are abundantly distributed within and outside the Sucquet-Hoyer canals.²⁴ The epithelioid or glomus cells are generally considered to be transversely sectioned muscle cells of the thick muscular wall of the anastomoses. They appear not unlike the ducts of sweat glands.¹³ The presence of argentophilic fibers coursing between the epithelioid muscle cells are characteristic of the anastomotic canals.

Although normal neuromyo-arterial glomus structures are distributed over the surface of the body, the hyperplastic growths are found less frequently in locations where the normal units are the most numerous. Grant and Bland⁶ studied normal adult fingers and found per square centimeter of skin surface on an average of 501 glomus units in the nail bed and 236 in the finger tips, the number decreasing rapidly in the central location. Greig,¹³ of Edinburgh, Scotland, the first to describe these tumors in the English literature, recorded 23 cases of glomus tumor, in only 1 of which the tumor was digital and that occurred on a finger. In 65 cases reports of which were collected by Bailey,²⁵ 21 of the tumors were subungual, only 1 of these being on the lower extremity. In the 62 cases reported by Stout,²⁶ 26 of 45 tumors of the upper extremity were subungual, while of 16 tumors of the lower extremities only 1 was subungual. In all 3 cases originally studied and identified by Masson, the tumor was in the nail bed of a finger.

Clinically, a glomus tumor is characterized by a small bluish subcutaneous nodule of unusual tenderness and paroxysms of localized or radiating pain, often of extreme severity. In Geschickter's series of cases the age varied from 18 to 82 years. However, Ireland,²⁷ at the Childrens Memorial Hospital in Chicago, verified by histologic study a glomus tumor excised from a child 9 years of age. The duration of

23. Lewis, Dean, and Geschickter, Charles F.: Glomus Tumors, *J. A. M. A.* **105**:775-778 (Sept. 7) 1935.

24. Lewis, T., and Pickering, G. W.: Vasodilatation in the Limbs in Response to Warming the Body with Evidence for Sympathetic Vasodilator Nerves in Man, *Heart* **16**:33-51 (Oct.) 1931.

25. Bailey, Orville T.: The Cutaneous Glomus and Its Tumors—Glomangiomas, *Am. J. Path.* **11**:915-936 (Nov.) 1935.

26. Stout, Arthur Purdy: Tumors of the Neuromyo-Arterial Glomus, *Am. J. Cancer* **24**:255-272 (June) 1935.

27. Ireland, Jay: Personal communication to the author.

symptoms may vary from two weeks, as in the case reported here, to thirty-seven years, as in Mason and Weil's case. As to sex distribution, Stout found that the great majority of the subungual tumors and tumors of the finger occur in females, while the tumors occurring elsewhere on the extremities are more frequent in males. Other authors report about an equal distribution.

Trauma is the only etiologic factor of significance. In about 50 per cent of the cases a history of injury is given. Many tumors, however, were without apparent cause. The locations where these nodules are commonly found lend themselves most easily to injury.

The benign character of a glomus tumor is substantiated by the fact that no recurrences have been reported after local excision. The tumor is not known to metastasize and is not invasive in its growth, although definitely demonstrated encapsulation is not always present. Prior to Masson's investigation such tumors were diagnosed as perithelioma, painful subcutaneous tumor,¹³ neurinoma and angiosarcoma (Kolaczek,²⁸ Kraske²⁹ and Carstensen³⁰). Occasionally, when the last diagnosis was made, amputation of the digit was recommended and performed. A more radical surgical procedure than local excision is unnecessary. Complete and permanent relief from symptoms and rapid healing of the wound follow local excision.

In most of the cases of glomus tumor heretofore recorded the condition was not recognized clinically. The numerous recent reports in medical literature will no doubt stimulate interest in the significance and importance of both the normal and the pathologic terminal arterio-venous anastomoses. This has already been noted by the thorough investigation of Popoff,⁵ who has identified changes in the terminal structures as characteristic of diabetes, senility and thrombo-angiitis obliterans. No further report has as yet substantiated his belief that senile and diabetic peripheral arterial diseases are not pathologically identical.

The normal glomus structures are unequally distributed over the surface of the body, being most numerous, however, on the fingers and toes. It is peculiar that hyperplasia with resulting tumor formation is found most frequently where the normal units are least numerous. Of the 65 collected cases reported by Bailey, in only 1 was the tumor subungual and located on the toe.

28. Kolaczek, J.: Ueber das Angiosarkom, *Deutsche Ztschr. f. Chir.* **9**:165-227 (Jan.) 1878.

29. Kraske, P.: Ueber subunguale Geschwülste, *München. med. Wchnschr.* **34**:889-891, 1887.

30. Carstensen, I.: Ueber subunguale Tumorem, *Arch. f. klin. Chir.* **144**:409-431, 1927.

The fact that in the case herewith recorded the nodule was not discovered until the peripheral circulation was increased had no etiologic significance. In more than 195 cases in which I have employed the same method of therapy no other tumor was discovered. Neither did Allen,³¹ of the Mayo Clinic, in approximately 250 cases, nor de Takáts³² in 100 cases, find a case of neuromyo-arterial glomus tumor. In Herrmann's³³ 600 cases of peripheral circulatory disease he found no glomus tumor. Scott³⁴ used positive and negative pressure therapy in 100 cases but in 2 cases of glomus tumor of the hand in which treatment was not directed to the peripheral arterial disease he excised the tumor. Landis³⁵ administered treatment in 225 cases without encountering a glomus tumor. These tumors remain small and are not known to become much larger than was found in my case. It is therefore reasonable to presume that the treatment or the resulting increase in the peripheral circulation was not responsible for the hyperplasia of the glomus structures. It is more likely that the adequacy of the circulation determines the clinical characteristics of a glomus tumor. Without sufficient blood in the anastomotic units, engorgement of the vessels does not take place, so that the presence of the tumor is overlooked. With overfilling of the vessels, bluish discoloration of the tumor occurs. The nerve endings, either within the anastomosis²⁵ or in the surrounding tissues,³⁶ are thereby stimulated with resulting exquisite pain and tenderness.

Histologic investigation of the neuromyo-arterial glomus has shown that the arteriovenous anastomosis is a direct offshoot from the cutaneous papillary vessels.³⁷ The structure is likened to a shunting process in which the amount of blood exposed to the cutaneous surface is controlled. Dilatation of the thick muscular-walled arteries (Succquet-Hoyer canal, fig. 4A) permits a varying amount of blood to be shunted directly back to the venous system. A similar anatomic arrangement of direct artery and vein connection in the wing of a bat was described by Paget.³⁸

Under pathologic conditions with tumor formation the congestion of the blood spaces produces a bluish swelling. The resulting pressure on the surrounding nerves gives rise to paroxysms of pain. Conversely,

31. Allen, E. V.: Personal communication to the author.

32. de Takáts, G.: Personal communication to the author.

33. Herrmann, Louis G.: Personal communication to the author.

34. Scott, W. J. Merle: Personal communication to the author.

35. Landis, Eugene: Personal communication to the author.

36. Hopf, Max: Neuromyo-Arterial Glomus Tumor (Masson), Frankfurt. Ztschr. f. Path. 40:387-399, 1930. Mason and Weil.¹² Masson.⁴

37. Grant and Bland.⁶ Masson.⁴ Picard.²¹

38. Paget, James, quoted by Todd, Robert B.: Cyclopedia of Anatomy and Physiology, London, Longman and others, 1852, vol 4, p. 1386.

contraction of the muscular walls of the vessels as a result of exposure to cold may compress the nerve fibers between the epithelioid cells of the vessel walls and produce pain. In this way the divergent observations of the effect of heat and cold on the painful paroxysms may be due to different physiologic processes.

Present knowledge of the cutaneous glomus is primarily the result of histologic investigation (Sucquet,¹ Hoyer,² Masson,⁴ Popoff,⁵ Grosser³). However, T. Lewis and his co-workers investigated these microscopic structures in order to explain their observation on the regulatory mechanism of the peripheral circulation. Lewis and Pickering,²⁴ and Grant and Bland⁶ expressed the belief that these anastomoses must be taken into account in dealing with peripheral circulation. In new-born and in elderly persons the cutaneous temperature regulation is poor. In these same groups the normal glomus units are poorly developed or atrophic and less numerous than in adults. Likewise, Grosser reported that reptiles, cold-blooded amphibians, are not supplied with them at all. This would be expected if the neuromyo-arterial glomus is definitely established as the regulatory mechanism of the peripheral circulation.

CONCLUSIONS

A subungual neuromyo-arterial glomus tumor of the toe occurring in a patient suffering from senile arteriosclerotic peripheral circulatory disease is herewith reported. Histologic examination confirmed the diagnosis of a glomus tumor.

The tumor was not discovered until the development of an excruciating painful crisis and exquisite tenderness of the toe. These symptoms followed improved circulation produced by treatments with alternating positive and negative pressure.

In more than 1,400 patients with peripheral circulatory disease treated with alternating positive and negative pressure no other glomus tumor was found.

In no other reported case of glomus tumor has a similar study of peripheral temperatures been made.

HEMANGIOMA OF A TENDON OR TENDON SHEATH

REPORT OF A CASE WITH A STUDY OF TWENTY-FOUR CASES FROM
THE LITERATURE

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CHICAGO

In 1930 Burman and Milgram¹ could find records of only sixteen cases of hemangioma of a tendon or of a tendon sheath, including six cases of their own and ten previously reported in the literature. In the present article a case is presented, and reports of eight more are collected from the literature, making the total of reported cases twenty-four. One of Burman and Milgram's cases is not included.

REPORT OF CASES

CASE 1 (Richet,² 1860).—A child aged 10 years complained of swelling of the lower two thirds of the right forearm of twenty months' duration. No murmur was heard on auscultation, but pressure could produce filling and emptying. A diagnosis of a venous erectile tumor was made, and treatment by injections of ferric chloride gave perfect results.

CASE 2 (Delagénière,³ 1894).—A seamstress aged 41 had noted seventeen years before operation that she had pain in the right wrist and swelling 5 cm. above the wrist. Two or three years later the tumor began to grow. At operation a cavernous hemangioma involving the extensor pollicis tendon was found.

CASE 3 (Schwartz,⁴ 1908).—A man aged 41 was injured sixteen months before operation with resultant persistent swelling over the right achilles tendon and interference with the movement of the right ankle. At operation an essentially capillary, partially cavernous hemangioma was found.

CASE 4 (Partsch,⁵ 1914).—A man aged 26, a land inspector, had swelling of the left forearm of three years' duration. Operation was performed. Because of recurrence one year later, there was a second operation.

CASE 5 (Weil,⁶ 1914).—A woman aged 23, a music teacher, had a painful swelling of the lower third of the flexor surface of the left forearm for five years

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1. Burman, M. S., and Milgram, J. E.: Hemangioma of Tendon and Tendon Sheaths, *Surg., Gynec. & Obst.* 50:397-406, 1930.

2. Richet, cited by Weil.⁶

3. Delagénière, cited by Weil.⁶

4. Schwartz: Ein Fall von fibromatöser Verdickung der Achillessehne, *München. med. Wchnschr.* 55:1235-1236 (June 9) 1908.

5. Partsch, cited by Weil.⁶

6. Weil, S.: Ueber peritendinöse Angiome, *Beitr. z. klin. Chir.* 88:56-68, 1914.

following an injury. Roentgen examination showed well defined opaque bodies, and at operation a cavernous hemangioma was found.

CASE 6 (Weil,⁶ 1914).—A maidservant aged 18 had nodules on the fingers of the left hand and on the left forearm since the first month of life. Roentgen examination showed a few definite phleboliths. At operation a cavernous hemangioma was found.

CASE 7 (Chauvin and Roux,⁷ 1920).—A young woman complained of swelling on the dorsum of the right foot following trauma, with the formation of a hematoma four years before operation. At operation a tumor attached to the extensor tendon of the fourth toe was found. Histologic examination revealed endothelial, cavernous hemangiomatous and fibrochondromatous tissue.

CASE 8 (Janik,⁸ 1927).—A married woman aged 40 had a painless swelling attaining the size of a fist on the right forearm of five years' duration. At operation endothelial, cavernous and fibrous tissue was found attached to the sheath of the flexor digitorum sublimis on the volar aspect of the forearm, and a diagnosis of hemangiofibroma was made.

CASE 9 (Burman and Milgram,¹ 1930).—A man, whose age was not stated, had pain in the left knee of six years' duration. Operation was performed. There was a recurrence of pain three and one-half years later, and another operation was performed. A cavernous hemangioma involving the left quadriceps tendon coincident with a port wine nevus of the base of the neck was found.

CASE 10 (Burman and Milgram,¹ 1930).—A girl aged 10 years had a growth on the palmar aspect of the distal portion of the left little finger and on the left wrist, which had been present since birth and a tumor on the left forearm which had been present for one year. Both were painless. When the finger was pricked, blood spurted more than from other fingers. The size changed with elevation and depression of the arm. Boiling water was injected into the tumor of the finger, and the tumor of the wrist was removed surgically, a cavernous hemangioma being found. An operation for recurrence of the tumor in the wrist and partial resection of the tumor in the forearm were performed one year later. In spite of roentgen therapy, there was subsidence of the condition but not complete cure.

CASE 11 (Burman and Milgram,¹ 1930).—A Negro girl aged 7 years had a growth on the outer side of the left leg of four years' duration. Operative removal of a cavernous hemangioma of the peroneus cuboideus tendon was performed, and there was no recurrence after seven months.

CASE 12 (Burman and Milgram,¹ 1930).—A woman aged 22 had a nodule in the left popliteal region of seventeen months' duration. Operative removal of a capillary hemangioma from the left semitendinous tendon was performed, and there was no recurrence after six months.

CASE 13 (Burman and Milgram,¹ 1930).—A man aged 57 had a painful swelling on the volar surface of the right wrist for two years. Operative removal of a capillary hemangioma attached to the flexor tendons was performed.

CASE 14 (Burman and Milgram,¹ 1930).—A woman aged 26 had a swelling on the leg for several years. Operative removal of a cavernous hemangioma of the plantaris tendon was performed. The side was not stated.

7. Chauvin and Roux: Fibro-chondroma de la gaine tendineuse de l'extenseur du quatrième orteil, *Bull. et mém. Soc. anat. de Paris* 90:75-77 (Feb.) 1920.

8. Janik, Alfred: Tumors of Tendon Sheaths, *Ann. Surg.* 85:897-911 (June) 1927.

ARCHIVES OF SURGERY

CASE 15 (Della Mano,⁹ 1932).—A woman aged 51 had multiple hemangiomas of the tendons of the left hand of seventeen years' duration. Roentgen examination revealed calcified granules in several of the tumors in the metacarpal and proximal phalangeal regions. At operation a mixed cavernous and capillary hemangioma was found.

CASE 16 (Principalli,¹⁰ 1932).—A housewife aged 14 had a swelling of the left foot for four years. At operation a partly cavernous hemangioma of the tendon of the peroneal muscle of the left foot was found.

CASE 17 (Grandclaude, Razemon and Bizard,¹¹ 1933).—A man aged 31 had noted a tumor as large as a "nut" near the anatomic snuff box several months before. Later there was sudden rupture of the tendon while using the hand. The side was not stated. Operative excision and tendon graft were performed, and a cavernous hemangioma attached to the long extensor of the thumb was found.

CASE 18 Botto Micca,¹² 1934).—A man aged 28, a bricklayer, had swelling of the dorsum of the right hand. Roentgen examination showed calcareous granules. At operation a cavernous hemangioma attached to the extensor tendons was found.

CASE 19 (Morton,¹³ 1934).—A man aged 21 had a previous operation for removal of a tumor the size of a walnut from the anterolateral aspect of the right wrist at the age of 4 years. There were recurrence at the age of 11, a painful period at the age of 13 and a return of pain several months before admission, but no change in the size of the swelling. Roentgen examination did not reveal any phleboliths or involvement of the bone. Operation revealed a tumor attached to two extensor tendons of the thumb. A cavernous fibrohemangioma was found on microscopic examination, and there was no recurrence after eleven months.

CASE 20 (Gottstein¹⁴).—The patient showed no recurrence ten years after operation.

CASE 21 (Furlkröges¹⁵).

CASE 22 (Koropovski¹⁶).

CASE 23 (Pitzorno¹⁷).

9. della Mano, N.: Angioma cavernoso delle guaine tendinee, Policlinico (sez. chir.) **39**:593-612 (Oct.) 1932.

10. Principalli, Silvio: Contributo alla conoscenza dei tumori vascolari delle guaine tendinee, Chir. d. org. di movimento **17**:128-132 (June) 1932.

11. Grandclaude, C.; Razemon, P., and Bizard, G.: Angio-lipoma arborescent de la gaine tendineuse du long extenseur du pouce ayant déterminé la rupture du tendon, Ann. d'anat. path. **10**:444-446 (April) 1933.

12. Botto Micca, Augusto: Contributo allo studio degli angiomi cavernosi dei tendini, Riv. san. siciliana **22**:568-577 (April 15) 1934.

13. Morton, J. J.: Tumors of the Tendon Sheaths: Their Close Biological Relationship to Tumors of the Joints and Bursae, Surg., Gynec. & Obst. **59**:441-452 (Sept.) 1934.

14. Gottstein, cited by Weil.⁶

15. Furlkröges, cited by Botto Micca.¹²

16. Koropovski, cited by Botto Micca.¹²

17. Pitzorno, cited by Tison and Hubert.²⁶

In reviewing these cases several borderline examples have not been included. Van Neck¹⁸ reported the case of a woman aged 56 with symptoms of pain in the left knee of less than one year's duration. Roentgen examination revealed an area of rarefaction about 1 cm. in diameter in the patella. At operation a hemangioma was found in this cavity. Despite its removal, the area of rarefaction persisted, as shown in subsequent roentgenograms. Although the patella is a sesamoid bone arising in a tendon, this case is not included in those of tumor arising in a tendon proper. Bouquet¹⁹ reported the case of a man, whose age was not stated, an electrician, with a swelling of the left forearm of two years' duration. Roentgen examination revealed definite small concentric opaque rings with relatively less opaque centers. Operation revealed that a cavernous hemangioma arose from the deep muscles and especially the interosseous membrane. Although this tumor arose primarily from the interosseous membrane, it is not considered to be of strictly tendinous origin.

Five cases of lymphangioma arising from a tendon or a tendon sheath have been reported in the literature, but they are not included in the group of hemangiomas proper. Princigalli¹⁰ reported the case of a woman aged 51, a housemaid, with a swelling of the volar surface of the base of the ring finger of at least seven weeks' duration. Operation revealed a lymphangio-endothelioma. Von Albertini²⁰ reported a case of lymphangioma of a tendon. Huguenin and Oberling²¹ reported two such cases. The first is that of an infant aged 3 years with a lymphangioma in the infrapatellar portion of the quadriceps tendon, which had been present since birth. The sex and the side of the body on which the swelling was located were not stated. Their second case was that of a man aged 47, a Lithuanian, with three tumors. One was on the palmar surface of the right ring finger and was considered too small to operate on. The other two were on the left hand, and on removal they were found to be lymphangiomas. As in the case of vascular tumors of other origin than from a tendon or a tendon sheath, the exact differentiation between hemangioma and lymphangioma is indistinct and somewhat arbitrary. In this regard the authors stated: "Les vaisseaux sanguins au voisinage de la tumeur sont très développés, et la présence de sang dans certaines cavités de la tumeur fait penser que des vaisseaux sanguins y sont fait irruption."

18. Van Neck, M.: Un cas d'angiome de la rotule, *Scalpel* 86:915-917 (June 17) 1933.

19. Bouquet, H., and DeBeayeu, A. Jambert: Un cas d'hémangioma primitif d'origine musculo-aponévrotique, *Arch. d'électric. méd.* 41:277-280 (July) 1933.

20. Von Albertini, cited by Grandclaude, Razemon and Bizard.¹⁷

21. Huguenin, R., and Oberling, C.: Lymphangiomes des tendons, *Bull. Assoc. franç. p. l'étude du cancer* 20:144-150 (Feb. 23) 1931.

(The blood vessels in the region of the tumor are greatly enlarged, and the presence of blood in certain cavities of the tumor leads one to conclude that extravasation has taken place.) Faldini²² reported a case of lymphangio-endothelioma of the tendon sheaths of the region of the ankle with metastatic tendencies. (This case is included in the total of sixteen instances of hemangioma collected by Burman and Milgram; it is not included in the present article.)

CASE 24 (Author's Case).—Miss R. K., aged 20, a housemaid of Swedish descent, entered the University of Chicago Clinics on Jan. 10, 1935, complaining of a painful swelling of the palmar surface of the left forearm of five months' duration. The onset of the condition was gradual, with no history of an antecedent injury. The growth of the swelling was steady, and during the past few months it was especially painful after the patient did her usual household duties. She believed that the left arm was becoming weaker than the right, and she "favored" it in her work. As an incidental complaint, she had been troubled with some nervousness and hyperhidrosis for several months.

Physical examination revealed a swelling about 5 cm. long and 3 cm. wide just above the wrist on the palmar aspect of the left forearm. This swelling was somewhat soft and semifluctuant and was not attached to the skin. It contained several hard nodules in its substance. It was somewhat movable, especially transversely, and did not seem to be attached to bone. The overlying skin was not discolored, but some of the neighboring veins were slightly enlarged. There was no thrill present, and auscultation was not performed. The length of the two forearms was equal; the circumference of the right was 23 cm., and that of the left, 21.5 cm. An incidental finding was the arterial blood pressure of 164 systolic and 98 diastolic, which was equal in the two arms. The urine, the white blood count and the hemoglobin content were normal. The Wassermann and Kahn reactions were negative. The basal metabolic rate was plus 16 on one examination and plus 7 on another.

Roentgen examination revealed no abnormality of the chest or neck. There was a soft tissue swelling of the ulnar and the flexor aspect of the left forearm just above the head of the ulna, in which there were areas of calcification, several as much as 2 mm. in diameter. A preoperative diagnosis of hemangioma of unknown origin was made.

Operation was performed on January 14 by Dr. H. Perry Jenkins. After the application of an elastic constrictor, which compressed blood out of the forearm, the tumor appeared to be definitely smaller. A longitudinal incision was made, and a bluish red tumor lying along the tendon of the flexor carpi ulnaris muscle was exposed. A superficial branch of the ulnar nerve and several blood vessels entered and coursed through the tumor and had to be ligated and removed. The constrictor was removed, bleeders were controlled and the wound was closed.

The patient was free from pain, and the wound healed promptly. A month after operation a small nodule was noted beneath the scar. This grew slowly and had become about 2 cm. in diameter and was elevated 1 cm. when it was excised, a year after the previous operation. At that time it was soft and not very compressible and did not change in size on elevation or depression of the arm or after shutting off the circulation by application of a blood pressure cuff. At the second operation (performed by me) the tumor was again adjacent to the

22. Faldini, cited by Burman and Milgram.¹

flexor tendons of the wrist but not definitely originating from any of them. The postoperative course was uneventful this time, and five months later there was no sign of recurrence.

Pathologic examination after the first operation showed the collapsed specimen to consist of a piece of meaty tissue measuring 3 by 2 by 2 cm. It was covered by a fibrous capsule under which small dark red lobules were seen. On palpation hard red nodules were felt within. Histologic examination revealed a fragment of dense fibrous tissue in which was found several areas containing endothelium-lined cavernous spaces containing red blood cells. In places there was slight hyperplasia of these endothelial cells. In the section which was prepared from the collapsed specimen, about one third of the tissue seemed to be composed of cavernous spaces and two thirds of fibrous tissue. In few regions was there

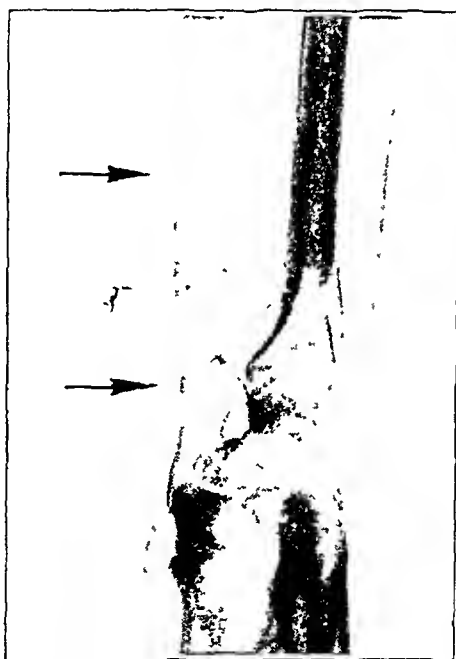


Fig. 1 (case 24).—Lateral roentgenographic view of the left wrist. The outline of the tumor is faintly seen on the volar surface, its upper and lower limits being marked by the arrows. In the substance of the tumor are seen several areas of calcification.

tissue resembling a capillary hemauglioma. In one section two rounded masses of living bone were seen lying next to a group of cavernous spaces. Figure 1 shows the cavernous spaces and adjacent living bone. The specimen obtained at the second operation was similar except that it contained no bone.

Two additional cases observed at the University of Chicago Clinics are not included in the foregoing series since the exact relation of the condition to a tendon or a tendon sheath was not conclusively proved. In the first of these additional cases, B. F., a high school student aged 17, complained of inability completely to flex or extend the right

elbow. He first noticed this while trying on a new coat. He had no pain until six months later, when there was a sudden onset of soreness, which lasted only a day or so. Again three weeks before admission there was considerable pain, and the arm was put in a cast for a week. On admission to the hospital there was marked tenderness over the head of the radius with marked interference with motion, but no tumor was palpable. On Aug. 16, 1935, the lateral epicondyle of the right humerus was exposed with the patient under general anesthesia. A soft vascular tumor about the size of a marble was found just anterior to the humerus, extending into the elbow joint, and was removed. It was situated so that flexion of the elbow would cause compression of the tumor. Histologic examination revealed a cavernous hemangioma. No recurrence was noted five weeks later, and there was marked increase in the range of motion of the elbow and no pain. The clinical diagnosis was cavernous hemangioma of the capsule of the right elbow joint.

The other case was that of D. M., a schoolgirl aged 11 years, who had a lump over the cord of the right heel for nine years. This had increased gradually in size during the past few years and was painful during the eight months preceding operation. It was slightly tender and elevated. It was not attached to the skin but seemed to be connected to the achilles tendon. The overlying skin was not discolored. The growth was 5 cm. above the insertion of the achilles tendon and measured 5 by 4 by 2.5 cm. Roentgen examination revealed a swelling of the soft tissue but no phleboliths. The mass was excised by Dr. C. H. Hatcher on July 23, 1934, and at operation was found to be only 2 cm. in diameter and connected with large subcutaneous veins and to the sheath of the achilles tendon. Histologic examination showed a cavernous hemangioma. There was no recurrence eight months later. The clinical diagnosis was cavernous hemangioma of the sheath (?) of the right achilles tendon.

COMMENT

Hemangioma of a tendon or of a tendon sheath is quite rare. Weil⁶ in 1913 collected reports of six such cases; Burman and Milgram¹ in 1930 were able to collect reports of sixteen; Botto Micca¹² in 1934 raised the total to nineteen, and in the present article twenty-four such cases are assembled. Hemangioma arising in a muscle is, on the other hand, much more common. Jenkins and Delaney²³ in 1932 collected two hundred and fifty-six such cases, and Nicolosi²⁴ and others have

23. Jenkins, H. P., and Delaney, P. A.: Benign Angiomatous Tumors of Skeletal Muscles, *Surg., Gynec. & Obst.* 55:464-480 (Oct.) 1932.

24. Nicolosi, Gioacchino: Sugli emangiomi primitivi dei muscoli striati, *Riv. san. siciliana* 22:32-41 (Jan. 1) 1934.

reported similar ones during the past three years. That hemangiomas of a tendon or of a tendon sheath comprise only a small fraction of all tumors of such origin is seen by a study of several reviews of all types of tumor of a tendon. King,²⁵ in his review of the pathologic structure of tumors of tendon sheaths, makes no mention of hemangioma. Tison and Hubert²⁶ referred to only one case of angioma in their review of the same subject. Morton's¹³ case as well as that of Janik,⁸ referred to earlier in this article, is taken from a large series of various types of tendon tumors. Lewis,²⁷ in reviewing the subject of tumor of a tendon sheath mentioned several types of tumor that have been reported in much greater numbers than the hemangioma considered in the present article. Ganglions of tendon sheaths are admittedly common. Lewis has reported over two hundred cases of giant cell tumor (xanthoma) of a tendon sheath, fifty of which were from his own laboratory of surgical pathology. He also found benign osteochondroma of a tendon quite common.

A study of the twenty-four cases of hemangioma of a tendon or of a tendon sheath reviewed in the present article reveals that in nineteen instances in which the sex was stated there were twelve females and seven males. The side on which the tumor occurred was stated in eighteen instances, the left being involved ten times and the right eight times. This does not indicate the marked preponderance of left-sided involvement mentioned by Burman and Milgram.¹ The upper extremity was involved thirteen times and the lower seven times. This is in opposition to the selective localization of hemangioma of the muscle in the lower extremity, as noted by Jenkins and Delaney.²³

Observation of change in size on elevation and depression of the limb and after application of a constrictor is of importance in the diagnosis. Roentgen examination, as in the case of hemangioma of the muscle,²³ will often reveal multiple calcified phleboliths. Positive findings in this regard were reported in five of the twenty-four cases (6, 10, 15, 18 and 24), as well as in Bouquet's case of hemangioma of a muscular aponeurosis. In only one instance (case 19) were no phleboliths found on roentgen examination. Pathologic examination, as in the case of hemangioma elsewhere in the body, cannot always clearly differentiate between the predominance of endothelial, of fibrous and of hemangiomatous involvement. Likewise, the line of demarcation between lymphangioma and hemangioma and also between capillary and cavernous

25. King, E. S. J.: Concerning the Pathology of Tumours of Tendon Sheaths, *Brit. J. Surg.* **18**:594-617 (April) 1931.

26. Tison, P., and Hubert, J.: Les tumeurs des gaines tendineuses, *Echo méd. du nord* **1**:943-953 (June 17) 1934.

27. Lewis, Dean: Tumors of Tendon Sheaths, *Surg., Gynec. & Obst.* **59**:344-349 (Sept.) 1934.

hemangioma must often be arbitrary. Three definite recurrences are mentioned (cases 4, 9 and 19), as well as two instances in which the operative removal was possibly not complete (cases 10 and 24). Surgical treatment, however, seems to be fairly efficacious, although many of the reported cases were not followed long enough to rule out recurrence.

CONCLUSIONS

A case of hemangioma of the flexor tendons of the wrist in a young woman is reported. Twenty-three other instances of hemangioma arising from a tendon or a tendon sheath are collected from the literature, making a total of twenty-four such cases. Hemangioma of this origin has a relatively benign clinical course, and operative removal seems to be the most efficacious form of treatment.

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PLATYSPONDYLY

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Platyspondyly is a congenital anomaly consisting essentially of a widening of the vertebral body, as is indicated by its derivation from the Greek terms *platy* meaning wide and *spondylos* signifying vertebra. This designation was coined in 1910 by Putti, who was the first to describe the deformity. The lesion was previously mentioned by Nau (1904) in his thesis on "Congenital Scoliosis," in which he described it as a widened bilobar vertebra. Subsequent to Putti's work, little mention was made of this anomaly save in the theses of Chevrier (1912) and Breton (1921). In 1927 Lance reported eight cases of this condition and definitely established it as a clinical entity. Further observations of this anomaly were made in France by Mouchet, Mauclaire, Botreau-Roussel, Clavelin, Tavernier and Massias. A search of the American and English literature failed to reveal a single report of this maldevelopment. Since I had the good fortune to encounter several instances of platyspondyly, I take the opportunity to report them and to discuss the pathogenesis, the clinical and roentgenographic appearances and the differential diagnosis of this condition.

For a clear understanding of this maldevelopment it is necessary to consider the embryology of the spine in its membranous, cartilaginous and osseous stages. The following description is based largely on the work of Bardeen.

EMBRYOLOGY OF THE VERTEBRAE

At a very early period in the development of the human embryo a layer of mesoderm appears between the ectoderm and the entoderm in the midsagittal plane. This mesodermal layer soon disappears from the region beneath the neural tube. Possibly it becomes incorporated with the entoderm in this region, which at this time presents a plate of tissue slightly thicker than its continuation on either side. This thickened entodermal plate is the chordal plate, which soon becomes pinched off from the entoderm to form the chorda dorsalis, about which the vertebrae and the intervertebral disks subsequently develop. Just

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before ossification of the vertebral bodies the chorda dorsalis disappears in its entirety, save for small fragments which remain to form the nuclei pulposi of the intervertebral disks.

At the time that the mesoderm disappears from the region of the chordal anlage, its lateral prolongations become divided into a series of segments known as mesoblastic somites. Concomitantly with the differentiation of the chorda dorsalis, the mesoblastic somites undergo a change. For a time, these consist of epithelial tissue which surround a central cavity known as the myoceles. Toward the end of the third week of embryonic life, the myoceles become gradually filled with branched spindle-shaped mesenchymal cells derived from the surrounding epithelium. The medial walls of the mesoblastic somites open, and the mesenchymal cells wander out toward the neural tube and chorda dorsalis, giving rise to a mass of tissue which ensheathes these structures. The mass of mesenchyme derived from each of these somites represents a sclerotome. The successive sclerotomes soon fuse so as to form a continuous mass of mesenchyme, one on each side, thus giving rise to the membranous stage in the embryonic development of the spine.

The division of the axial mesenchyme in segments which are known as sclerotomes, and which correspond to the myotomes, is marked off at an early stage by intersegmental arteries. At this time each sclerotome becomes divided into two portions, a caudal half and a cranial half. A slight fissure—the intersegmental fissure—may partially separate the two halves. From the caudal half arises the primitive vertebra of Remak, or scleromere, with dorsal (neural), ventral (costal) and chordal processes. The latter unite these structures to the perichordal sheath, which is a dense membrane about the chorda dorsalis. From the cranial halves of the sclerotomes arise the interdorsal membranes, which unite the dorsal (neural) processes, and the interventral membranes, which unite the ventral (costal) processes. The chordal processes give rise to the primitive intervertebral disks. The tissue lying between each two disks now becomes completely surrounded by a membrane, the interdiskal membrane. Meanwhile the perichordal sheath between each two disks becomes extended ventrodorsally, so that it gives rise to a perichordal septum, which divides into two parts the space surrounded by the interdiskal membrane.

The cartilaginous stage begins at this time with the appearance at about the same time in the aforementioned membranous vertebra of six primary centers of chondrification, one for each costal process, one for each neural arch and one for each half of the vertebral body. The costal processes do not retain their connection with the body of the vertebra but soon break away to form rib cartilages. At first

the cartilage of one side of the vertebra, which is formed by a transformation of the loose tissue lying between the primitive intervertebral disks surrounded by the interdiskal membrane, is separated from that of the other side by the perichordal septum. This is soon broken through, and the two cartilaginous anlagen of the vertebral body become united about the chorda. Processes then grow out from the vertebral arch to form transverse and articular processes, and each half of the vertebral arch meets its fellow of the opposite side to form a spinous process.

The osseous stage begins with the appearance of centers of ossification for the neural arches and costal processes in correspondence with the original cartilaginous centers. The centers of ossification of the bodies in most of the vertebrae show little evidence of the bilateral origin of the centers of chondrification.

For the purposes of this paper it is necessary to note the following phases in the membranous stage of the embryologic development of the spinal axis: (1) the division of the axial mesenchyme into sclerotomes equal in number to and corresponding with the myotomes; (2) the subdivision of each sclerotome into a cranial and a caudal portion; (3) the fusion of the cranial and caudal halves of the adjoining sclerotomes to form the primitive vertebrae; (4) the presence of the perichordal septum which divides each vertebral anlage into two lateral halves, and (5) the fusion of the lateral halves to form the final vertebra. It is therefore evident from the foregoing data that aberrations of the processes of axial segmentation or subsequent fusion will cause anomalies of differentiation, morphology and numerical variations. Furthermore, failure or delay of fusion of the lateral halves causes hemivertebrae and the three types of platyspondyly to be described later.

PATHOGENESIS OF PLATYSPONDYLY

Putti noted the maldevelopment under discussion only in the fourth and fifth lumbar vertebrae. In each instance it was associated with spina bifida, i. e., failure of fusion of the posterior arch. His explanation of this characteristic appearance is that it is caused by an actual widening of the vertebral body in addition to an apparent widening of the body due to the shadows cast by the articular and transverse processes resulting from the spreading of the neural arches, because of failure of union of the lateral halves of the neural arches at the spinous processes. Perussia in his case report agreed with Putti's explanation of this congenital anomaly.

Lance, however, noted this maldevelopment in other regions of the spine, in association at times with spina bifida and somatoschisis, i. e., a failure of fusion of the lateral halves of the vertebral bodies. He

also reported two cases of total involvement of the spine. Lance expressed the belief that this anomaly is caused by a failure or a delay of fusion of the lateral halves of the vertebral anlagen in the membranous stage of their embryologic development. Thus a failure of fusion of the posterior arches causes spinal bifida, and a failure of fusion of the vertebral bodies causes somatoschisis, while a delay of fusion causes the widening of the vertebral bodies with their characteristic appearances, to be described later. With this developmental basis for his theory, Lance was enabled to classify this anomaly into several types.

It appears to me and to most contributors to this subject that Lance's conception of platyspondyly explains all the variations of this condition and is in harmony with the results of embryologic studies. Putti's views on the pathogenesis are insufficient, because he did not include the various forms of this condition. Furthermore, spina bifida occulta and spina bifida completa are not necessarily accompanying anomalies. It is also pointed out that spina bifida may occur in the same embryonic (membranous) stage as somatoschisis or during the ossific stage. In the former case it is the result of the same cause as platyspondyly, but if it occurs merely as a result of failure of bone fusion it is a result rather than the cause of platyspondyly.

The three types of platyspondyly described by Lance present the following picture:

Type 1. The anomaly of this type consists of a widened vertebra, thickened, adjacent vertebral disks and spina bifida, as described by Putti. This form is localized and usually involves the fourth and fifth lumbar vertebrae.

Type 2. In this type there is a widened vertebral body which is divided into two cuneiform segments, with their apexes placed centrally and their bases laterally. This anomaly may or may not be associated with spina bifida. In this type spina bifida and somatoschisis are rarely limited to one segment and are associated with anomalies in number, regional differentiation and fusions of vertebrae. Platyspondyly of this type is most common in the dorsal and cervicodorsal regions of the spine. In such cases the shape of the intervertebral disks is the counterpart of the shape of the vertebrae.

Type 3. In this type the superior and inferior surfaces of the vertebral bodies are concave in the center, as seen in the anteroposterior views, while the intervertebral disks are convex and proportionally higher than normal. Such an anomaly may be limited to several vertebrae or may involve the entire spine.

DESCRIPTION OF TYPES OF PLATYSPONDYLY

Type 1, which is characterized by a widened vertebra, diminished vertical diameter and spina bifida posterior, is usually limited to the

fourth and fifth lumbar segments. The adjacent intervertebral disks are usually increased in height. The instances of this type are usually discovered accidentally. A person with this type of platyspondyly has a potentially weak back, and may present neurotrophic symptoms due to the spina bifida. This type may, or more often may not, be accompanied by other congenital anomalies. Marziani found this form of platyspondyly in 17 per cent of his cases of spina bifida. Cases 1 to 5, inclusive, that are reported here are examples of this group.

Type 2, the localized form described by Lance, which presents somatoschisis with or without spina bifida, is characterized clinically by weakness of the back, vague pains and varying degrees of deformities of the spine found in congenital scoliosis and kyphosis. This form is usually localized at the cervicodorsal and dorsal regions and is often associated with spinal anomalies of differentiation, morphology and number. *It may also be associated with congenital maldevelopments of the ribs, elevated scapulae (Sprengel's deformity) and the short neck syndrome (Klippel-Feil's syndrome).* At times there may be found neurotrophic disturbances due to the spina bifida. When the deformities are severe, death occurs during fetal life. It would seem, from my observation of the many case reports in which platyspondylitic anomalies are recorded without being named as such, that this form is much more common than is indicated in the literature. It is true that this may be merely of academic import; nevertheless, it is important to recognize this type, so as to form a complete picture with those forms of platyspondyly that are of clinical importance. Cases 6 to 13, inclusive, are illustrative of this type.

Type 3 is present clinically in two forms, the generalized and the localized form. The generalized form is rare. Lance described two cases. Tavernier and Massias reviewed these and added two more instances. Marziani added another case, and Benoiste-Pilloire and Gourdon added still another. In all, six cases have been described heretofore. I am reporting five additional cases (cases 13 to 17, inclusive). This type of platyspondyly is a distinct clinical entity and can be readily recognized by its roentgenographic appearance. The clinical picture, however, may at times be so definite as to suggest this condition. The outstanding and practically the only symptom is an unusual flexibility of the spine, noted in infancy, so much so that the patient cannot stand without support. In the sitting position the infant presents a long posterior curve and a forward inclination of the body because of inability to support the head and trunk. Roentgenographically, the picture is equally characteristic. The anteroposterior roentgenograms show all of the vertebral segments to be abnormally widened, their vertical diameters lessened by one half to one third of the normal

height and their superior and inferior vertebral outlines concave in the midregion. At the same time the intervertebral disks are correspondingly increased in height, and their superior and inferior surfaces are convex to correspond to the vertebral concavities. The entire picture has the appearance of alternating biconvex, abnormally high, wide and clear disks with biconcave, abnormally wide, low and darker segments—the vertebral bodies. The lateral views show little save the disproportion in the vertical diameters of the disks and bodies. The outlines of the vertebrae and disks are sharp and clear, and their texture is normal in appearance. This type usually presents no other roentgenographic congenital abnormalities. Benoiste-Pilloire and Gourdon's case is exceptional in that in addition to the spinal maldevelopment there was bilaterally an absence of all of the bones of the wrists, absence of the tarsal scaphoid and two cuneiform bones, enlargement of the acetabula and a trophic disturbance of the head of the femurs.

The localized form is also distinct and presents an appearance similar to the generalized form, save that the lesion is localized to one or more segments of the spine. These segments may appear occasionally as fusiform widenings of the spine, with the greatest widths at the center and a gradual diminution of the width as the upper and the lower pole of the segments are approached. If the lesion is at the upper or lower end of the spine, the appearance may be that of a half of a fusiform swelling, with the greatest width at either the upper or the lower end of the spinal column. The characteristic concavities on the superior and inferior surfaces of the vertebral bodies are not likely to be as well marked as in the generalized form. The localized form is likely to be associated with cervical ribs, hypertrophied transverse processes of cervical vertebrae and failure of descent of one or both scapulae. Clinically, they are symptomless *per se*. Cases 18 to 39, inclusive, are examples of this form.

It is not to be assumed that this classification into types is clearcut. The most distinct groups are type 2 and the generalized form of type 3. The differentiation of type 1 from the localized form of type 3 may sometimes be arbitrary, as will be shown by cases 18 and 19, in which there was a combination of both subdivisions.

Marziani agreed with the foregoing conceptions only so far as types 1 and 2 are concerned. According to him, type 3 is a microspandyly of chondrodystrophic or osteochondroplastic origin, associated with a flattening of the vertebral bodies rather than with true congenital platyspandyly. Marziani, however, failed to explain how the typical concavities of the superior and inferior vertebral borders are produced in the so-called instances of chondrodystrophy and osteochondroplasty. I have noted several forms of chondrodystrophy with

a generalized platyspondyly, but these can be readily differentiated, as will be noted later. Furthermore, no instance of generalized osteochondropathy of the spine has ever been noted. The localized forms can be readily differentiated, as will be indicated in the following discussion.

DIAMETERS OF NORMAL VERTEBRAE

It is opportune at this point to consider the normal ratios of the transverse diameters to the vertical diameters of the various vertebrae and their relations to each other. An extensive search of the literature revealed but few references to this subject. Alban Kohler stated that beginning with the first cervical segment each successive vertebral body is higher than, or at least equal in height to, the one above it. Any lessening of the vertical diameter in a caudal segment is pathologic. This, he stated, holds true for all vertebrae, with the exception of the fifth lumbar segment. Hans Jacobi, of Schmorl's Clinic, on the basis of his measurements of one hundred and two spines, including the first dorsal to the third lumbar segments, of persons between the ages of 18 to 87, stated that each caudal vertebra is higher than the one above it, save the sixth dorsal segment, which is 1 mm. less than the fifth dorsal vertebra. Anderson quoted Henle to the effect that the vertical diameter increases from the third cervical to the last lumbar vertebra. On the basis of his own measurements of anatomic material, he found that the fifth dorsal vertebra has the smallest transverse diameter and that a gradual increase in the transverse diameter takes place from the second cervical to the second dorsal vertebra, followed by a gradual increase to the fifth lumbar segment. He also appended a table of the means of the transverse and the vertical diameters of the bodies of fifty-three vertebral columns. I have calculated the ratios of the transverse diameters to the vertical diameters as shown in table 1. Cyriax is the most recent writer to measure a series of vertebral columns. He also gave the transverse and vertical means of anatomic material. I have reduced these to the ratios of the transverse to the vertical measurements, as shown in table 1.

A consideration of this material has shown it to be insufficient for my purposes, for the aforementioned authors did not consider the variations that might possibly exist at various ages. In fact, the age variant was not mentioned by these writers. Furthermore, their observations were made on anatomic material, while the present study is based on roentgenographic appearances. I felt, therefore, that it was incumbent on me to make measurements on roentgenograms of normal spines at various ages. One hundred and forty-five series of roentgenographic films of whole or partial spines were measured in the anteroposterior and lateral views. Since only ratios are being con-

sidered, the variant of distance of exposure is of no consequence. The one hundred and forty-five spines were divided into six age groups—birth to 1 year of age, 1 to 6 years, 6 to 11 years, 11 to 16 years, 16 to 22 years and 22 years of age and over, as shown in table 2.

TABLE 1.—*Ratios of the Transverse Diameters to the Vertical Diameters of Normal Vertebral Bodies*

Author.....	Cyrlax	Anderson*	Buchman
Age.....	Adult	Adult	22 and Over
Material	Autopsy	Autopsy	Roentgenograms
C- 1.....
C- 2.....	...	1.0	...
C- 3.....	1.6	1.6	1.8 (4)†
C- 4.....	1.7	1.8	1.9 (7)
C- 5.....	1.9	1.9	1.9 (8)
C- 6.....	2.1	2.2	2.0 (10)
C- 7.....	2.2	2.1	2.0 (12)
D- 1.....	2.0	1.8	1.8 (14)
D- 2.....	1.8	1.7	1.8 (16)
D- 3.....	1.7	1.5	1.6 (15)
D- 4.....	1.5	1.4	1.4 (11)
D- 5.....	1.5	1.4	1.5 (11)
D- 6.....	1.5	1.5	1.5 (12)
D- 7.....	1.5	1.5	1.5 (12)
D- 8.....	1.6	1.5	1.5 (12)
D- 9.....	1.5	1.5	1.6 (12)
D-10.....	1.6	1.6	1.5 (12)
D-11.....	1.7	1.5	1.5 (14)
D-12.....	1.6	1.6	1.5 (14)
L- 1.....	1.6	1.7	1.4 (19)
L- 2.....	1.6	1.7	1.4 (19)
L- 3.....	1.6	1.8	1.5 (19)
L- 4.....	1.7	1.9	1.6 (19)
L- 5.....	1.7	2.1	1.8 (11)

* Anderson's work is based on fifty-three spines.

† The numbers in parenthesis indicate number of observations.

TABLE 2.—*Ratios of the Transverse Diameters to the Vertical Diameters of Normal Vertebral Bodies**

Age Group	Birth to 1 Year	1 to 6 Years	6 to 11 Years	11 to 16 Years	16 to 22 Years	22 Years and Over
C- 2.....	1.9 (6)†	1.7 (1)	2.2 (1)
C- 3.....	2.1 (11)	2.2 (1)	2.2 (1)	2.1 (3)	1.8 (4)
C- 4.....	2.0 (11)	2.0 (1)	2.3 (1)	2.4 (7)	1.9 (6)	1.9 (7)
C- 5.....	1.9 (13)	2.0 (1)	2.3 (3)	2.5 (9)	1.9 (7)	1.9 (8)
C- 6.....	2.0 (12)	2.3 (2)	2.2 (7)	2.4 (12)	2.2 (9)	2.0 (10)
C- 7.....	2.1 (12)	2.3 (3)	2.2 (9)	2.2 (15)	2.2 (11)	2.0 (12)
D- 1.....	2.1 (12)	2.1 (5)	2.2 (10)	2.2 (19)	2.0 (10)	1.8 (14)
D- 2.....	2.2 (13)	2.1 (7)	2.2 (10)	2.0 (20)	1.9 (11)	1.8 (16)
D- 3.....	2.3 (14)	2.0 (11)	1.9 (13)	1.7 (20)	1.7 (11)	1.6 (15)
D- 4.....	2.2 (15)	1.9 (11)	1.8 (13)	1.6 (21)	1.5 (9)	1.4 (11)
D- 5.....	2.5 (17)	1.9 (11)	1.7 (12)	1.5 (22)	1.4 (8)	1.5 (11)
D- 6.....	2.4 (21)	1.8 (11)	1.8 (12)	1.5 (23)	1.4 (8)	1.5 (12)
D- 7.....	2.5 (23)	1.8 (11)	1.7 (13)	1.5 (23)	1.4 (9)	1.5 (12)
D- 8.....	2.5 (27)	1.8 (12)	1.8 (13)	1.5 (23)	1.5 (8)	1.5 (12)
D- 9.....	2.5 (28)	1.9 (12)	1.8 (14)	1.5 (23)	1.5 (9)	1.6 (12)
D-10.....	2.3 (30)	1.9 (13)	1.8 (14)	1.6 (23)	1.5 (9)	1.5 (12)
D-11.....	2.3 (36)	1.9 (14)	1.9 (14)	1.6 (23)	1.5 (12)	1.5 (14)
D-12.....	2.3 (38)	1.9 (14)	1.9 (14)	1.6 (24)	1.4 (12)	1.5 (14)
L- 1.....	2.2 (39)	1.8 (14)	1.7 (14)	1.6 (24)	1.4 (14)	1.4 (19)
L- 2.....	2.1 (39)	1.8 (14)	1.8 (12)	1.6 (23)	1.4 (15)	1.4 (19)
L- 3.....	2.2 (39)	1.9 (14)	1.8 (11)	1.6 (21)	1.4 (13)	1.5 (19)
L- 4.....	2.2 (35)	1.9 (14)	1.9 (10)	1.7 (18)	1.6 (12)	1.6 (19)
L- 5.....	2.3 (29)	2.1 (10)	1.9 (8)	2.0 (6)	1.7 (8)	1.8 (11)

* Calculated from my measurements on roentgenograms of one hundred and forty-five patients.

† The numbers in parenthesis indicate the number of observations.

A comparison of the ratios obtained for the spines of patients 22 years of age and over with the ratios obtained from the observations of Cyriax and Anderson, which I feel justified in assuming to be based on adult material, shows insignificant variations which are not greater than those found between the figures of the latter authors (table 1). It is therefore apparent that the ratios obtained from the measurements of transverse and vertical diameters on roentgenograms are sufficiently accurate for practical purposes. It is to be noted that beginning with the second cervical segment the ratio increases gradually to the sixth and seventh cervical vertebrae, and then there is diminution, which reaches its maximum at the fourth and fifth dorsal segments, to be followed by an increase in the ratio of transverse and vertical measurements, reaching a maximum at the fifth lumbar vertebra. The greatest ratio obtained in these three sets of observations is 2.2 for the sixth cervical segment.

A study of the figures for the other groups of patients (table 2) shows that the ratios are highest for the age group from birth to 1 year. These ratios decrease until the adult age is reached.

MEASUREMENTS OF NORMAL VERTEBRAL DISKS

Greater difficulties were met in an attempt to learn the normal ratios of the heights of the intervertebral disks to the vertebral bodies and their relationship to one another. A study of the literature revealed only general statements, as those of Piersol, who stated in his "Human Anatomy" that the disks form 40 per cent of the cervical region, 20 per cent of the thoracic segment and 33 per cent of the lumbar portion of the spine. Hans Jacobi is the only author who to my knowledge presented detailed data based on measurements of a large series of spines (one hundred and two) removed at autopsy, including the region between the first dorsal and the third lumbar segment, as shown in table 3.

I considered these data insufficient, for Jacobi was concerned with anatomic material while my study is based on roentgenographic appearances. I, therefore, made measurements and calculated the ratios for the various age groups (table 4).

A comparison of the measurement of the spines of patients 22 years of age and over with the measurements of Jacobi show slight variations. I feel, nevertheless, that roentgenographic measurements of disks cannot be accurate, for there are several factors of error owing to the smallness of the measurements and the variations in the shape of disks *resulting from positions of flexion and extension and variations incidental to points of measurements*. I therefore look on the figures as only approximately correct.

A study of the ratios obtained for the younger age groups reveals that here also these ratios are greatest for the age group from birth to 1 year and that these ratios decrease until an adult age is reached (table 4).

TABLE 3.—*Ratios of the Vertical Diameters of the Subjacent Intervertebral Disks to the Vertical Diameters of Normal Vertebral Bodies*

Author.....	Jacobi*	Buehman
Material.....	Autopsy	Roentgenograms
Age.....	Adult	22 Years and Over
C-1.....
C-2.....
C-3.....	0.4 (2)†
C-4.....	0.4 (3)
C-5.....	0.45 (3)
C-6.....	0.4 (3)
C-7.....	0.3 (5)
D-1.....	0.25	0.2 (3)
D-2.....	0.23	0.25 (4)
D-3.....	0.21	0.2 (4)
D-4.....	0.20	0.2 (5)
D-5.....	0.20	0.2 (5)
D-6.....	0.21	0.2 (6)
D-7.....	0.20	0.2 (6)
D-8.....	0.24	0.25 (6)
D-9.....	0.24	0.25 (6)
D-10.....	0.25	0.25 (6)
D-11.....	0.25	0.25 (8)
D-12.....	0.27	0.3 (8)
L-1.....	0.32	0.3 (9)
L-2.....	0.33	0.3 (10)
L-3.....	0.37	0.3 (10)
L-4.....	0.3 (10)
L-5.....	0.3 (5)

* Jacobi's work is based on one hundred and two spines.

† The numbers in parenthesis indicate the number of observations.

TABLE 4.—*Ratios of the Vertical Diameters of the Subjacent Intervertebral Disks to the Vertical Diameters of Normal Vertebral Bodies**

Age Group	Birth to 1 Year	1 to 6 Years	6 to 11 Years	11 to 16 Years	16 to 22 Years	22 Years and Over
C-1.....
C-2.....	0.4 (5)†
C-3.....	0.4 (7)
C-4.....	0.4 (8)	0.5 (2)	0.4 (1)	0.4 (3)
C-5.....	0.3 (9)	0.3 (1)	0.4 (3)	0.4 (1)	0.45 (3)
C-6.....	0.4 (10)	0.3 (2)	0.4 (3)	0.4 (2)	0.4 (3)
C-7.....	0.4 (10)	0.3 (4)	0.3 (3)	0.4 (4)	0.3 (5)
D-1.....	0.4 (10)	0.3 (3)	0.3 (4)	0.3 (4)	0.3 (3)	0.2 (3)
D-2.....	0.5 (11)	0.3 (4)	0.3 (8)	0.2 (6)	0.3 (3)	0.25 (4)
D-3.....	0.5 (12)	0.3 (6)	0.2 (9)	0.2 (7)	0.3 (3)	0.2 (4)
D-4.....	0.5 (13)	0.3 (7)	0.2 (9)	0.2 (7)	0.3 (4)	0.2 (5)
D-5.....	0.6 (15)	0.3 (7)	0.3 (10)	0.2 (7)	0.3 (4)	0.2 (5)
D-6.....	0.6 (19)	0.3 (7)	0.3 (10)	0.2 (10)	0.2 (5)	0.2 (6)
D-7.....	0.5 (21)	0.3 (7)	0.2 (10)	0.2 (10)	0.2 (5)	0.2 (6)
D-8.....	0.4 (25)	0.3 (8)	0.3 (10)	0.2 (10)	0.2 (5)	0.25 (6)
D-9.....	0.45 (26)	0.3 (8)	0.2 (11)	0.2 (10)	0.2 (6)	0.25 (6)
D-10.....	0.4 (28)	0.3 (9)	0.3 (11)	0.2 (10)	0.2 (6)	0.25 (6)
D-11.....	0.4 (34)	0.3 (9)	0.3 (11)	0.2 (10)	0.3 (6)	0.25 (8)
D-12.....	0.4 (36)	0.3 (9)	0.3 (11)	0.3 (9)	0.3 (7)	0.3 (8)
L-1.....	0.4 (37)	0.3 (9)	0.4 (10)	0.3 (8)	0.3 (7)	0.3 (9)
L-2.....	0.4 (37)	0.4 (9)	0.4 (7)	0.3 (8)	0.3 (8)	0.3 (10)
L-3.....	0.4 (37)	0.4 (9)	0.5 (7)	0.4 (6)	0.3 (7)	0.3 (10)
L-4.....	0.4 (33)	0.4 (9)	0.5 (5)	0.4 (5)	0.3 (6)	0.3 (10)
L-5.....	0.3 (24)	0.4 (4)	0.4 (5)	0.4 (2)	0.3 (2)	0.3 (5)

* Calculated from my measurements on roentgenograms of one hundred and forty-five patients.

† The numbers in parenthesis indicate the number of observations.

MEASUREMENTS OF THE VERTEBRAL AND INTERVERTEBRAL
DISKS IN PLATYSPONDYLY

Table 5 represents the ratios obtained in thirty-eight cases of platyspondyly and is indicative, as is evidenced by the increase in the ratios, of the disturbance in the relationship between the transverse and the vertical diameter of these patients. This disturbance becomes self-apparent when compared with the normal ratios for the various age groups given in tables 2 and 4.

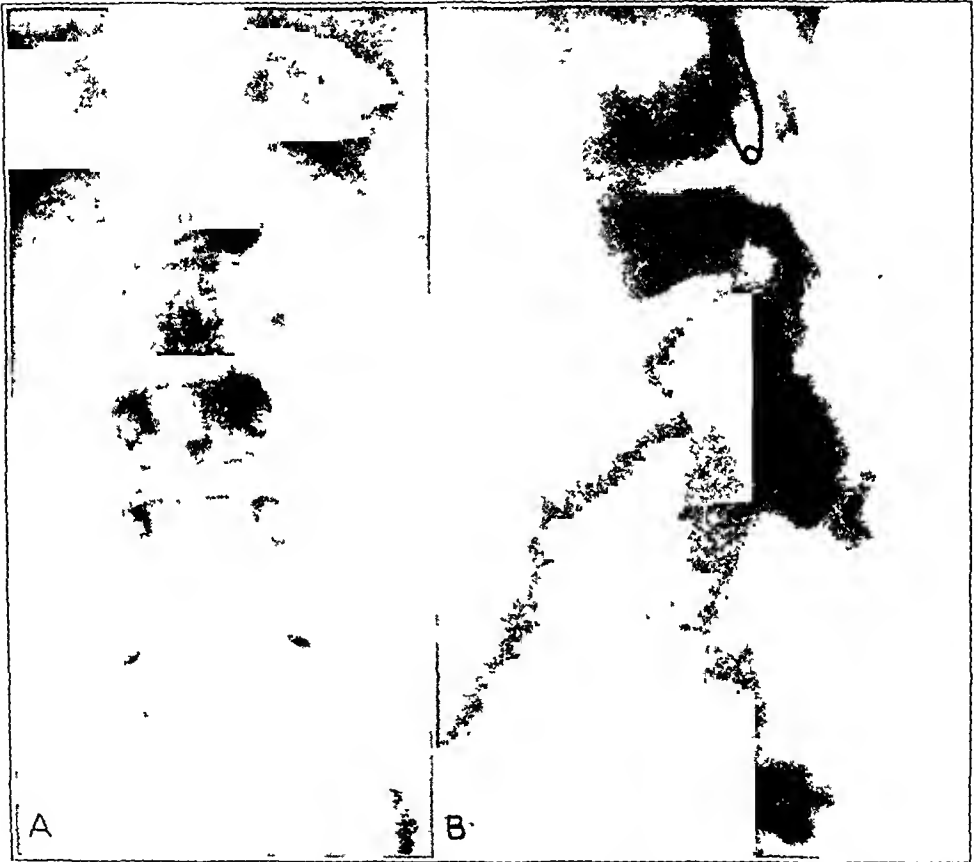


Fig. 1 (case 1).—Platyspondyly, type 1. In *A*, the fifth and to a lesser extent the fourth lumbar vertebra are widened transversely. In *B*, the vertical diameter of the fifth lumbar vertebra is less than normal.

CASES OF TYPE 1

CASE 1—A. H., an American-born white boy, 12 years of age, was admitted to the service of Dr. Samuel Kleinberg at the Hospital for Joint Diseases because of multiple foci of osteomyelitis, among which was included the left sacro-iliac joint.

As an incidental finding, spina bifida occulta of the fifth lumbar vertebra was noted in the anteroposterior roentgenogram (fig. 1*A*). The fifth vertebral segment and, to a lesser extent, the fourth, were widened transversely. The lateral view (fig. 1*B*) showed distinctly the lessening of the vertical diameter of the fifth lumbar vertebra.

TABLE 5.—*Ratios of the Transverse Diameters to the Vertical Diameters of the Vertebral Bodies and Ratios of the Vertical Diameters of the Subjacent Intervertebral Disks to the Vertical Diameters of the Vertebral Bodies in Platyspondyly**

Case.....	1	2	3	4	5	6	7	8	9	10	11	12
Age.....	12 Years	5 Years	5 Years	6 Years	12 Years	5 Years	10 Months	14 Years			18 Years	7 Years
	Vert. Disk	Vert. Disk	Vert. Disk	Vert. Disk	Vert. Disk	Vert. Disk	Vert. Disk	Vert. Disk	Vert. Disk	Vert. Disk	Vert. Disk	Vert. Disk
O-2.....	3.7
O-3.....	7.6	..	5.0	3.7
O-4.....	5.8	..	5.0	3.3
O-5.....	4.6	2.2	..	5.2
O-6.....	4.6	4.8	3.6	3.7	..	2.9
O-7.....	3.1	2.8	3.9	3.4	..	3.0
D-1.....	4.0	2.0	4.2	4.3	..	2.5
D-2.....	2.2	2.6	7.6	2.8	..	1.7
D-3.....	2.8	0.3	3.6	2.1
D-4.....	2.3	0.4	2.8	2.2
D-5.....	1.7	..	1.8
D-6.....	1.5	..	1.6
D-7.....	1.6	..	2.5
D-8.....	1.5	..	1.9
D-10.....	2.7
D-11.....	2.7
D-12.....	2.1
L-1.....	1.7	1.2	1.7	0.1	..
L-2.....	1.7	0.3	1.3	1.8	0.1	..
L-3.....	1.9	0.4	1.8	1.8	0.1	..
L-4.....	2.0	0.4	2.6	0.3	0.3	1.6	0.1	..
L-5.....	2.5	0.4	2.4	0.5	2.9	0.5	1.4	0.1	..
Comment...	Spina bifida occulta of L-5		Spina bifida occulta of upper sacral segments		Spina bifida occulta of L-3 and S-1		Cervical rib at C-7; somato-schisis of C-5, 6, 7	Congenital scoliosis; fusion of D-3 and D-4	Hemivertebral between C-6 and C-7; bilateral Sprengel's deformity	Bilateral cervical ribs; seventh rib atrophic; spina bifida occulta of D-6, 7 and 8; somato-schisis of S-1	Fusion of anterior halves of D-12 to and of C-7; including L-4; spina bifida occulta of S-1	Hyper-trophied transverse processes of C-7; somato-schisis of C-5; congenital torticollis
Case.....	13	14	15	16	17	18	19	20	21	22	23	24
Age.....	3½ Years	20 Months	2 Years	12 Months	18 Months	6 Years	6½ Years	9 Years	8 Years	7 Years	3½ Years	8 Years
	Vert. Disk	Vert. Disk	Vert. Disk	Vert. Disk	Vert. Disk	Vert. Disk	Vert. Disk	Vert. Disk	Vert. Disk	Vert. Disk	Vert. Disk	Vert. Disk
G-2.....	4.4
G-3.....	5.5	8.3	4.4	..	4.6	..	3.9	5.0
G-4.....	0.7	1.3	..	8.3	4.4	..	7.0	..	3.6	0.4
G-5.....	6.7	6.3	4.6	..	12.7	..	2.9	3.4	..	5.4
G-6.....	3.3	0.5	0.7	..	0.3	..	0.5	0.6	..	1.0
G-7.....	7.0	1.0	3.3	0.5	3.8	..	0.4	..	2.9	0.7	..	4.1
D-1.....	5.2	0.8	3.0	0.4	3.4	2.6	0.3	..	3.0	0.6	4.1	1.0
D-2.....	5.6	0.8	3.0	0.4	3.3	2.6	0.3	..	2.5	0.3	3.1	0.7
D-3.....	4.1	0.8	2.5	0.3	3.0	2.4	0.6	..	3.0	0.4	2.9	0.4
D-4.....	3.8	0.8	2.4	0.4	2.4	2.4	0.4	2.1	1.9	0.2	2.0	0.3
D-5.....	3.8	0.7	2.4	0.4	2.4	2.3	0.3	1.8	1.7	0.1	2.3	0.2
D-6.....	3.0	0.5	2.5	0.4	2.5	1.8	..	1.9	1.7	0.3	1.9	0.1
D-7.....	3.0	0.5	2.5	0.4	2.5	1.7	..	1.6	1.7	0.3	1.8	0.2
D-8.....	3.0	0.6	2.5	0.4	2.5	1.7	..	1.6	1.6	0.2	1.8	0.1

	26	0.4	2.5	0.3	2.5	0.4	2.8	0.4	2.5	0.5	1.6	0.2	1.7	0.3	1.8	0.1	..
D-9.....	2.6	0.4	2.3	0.3	2.3	0.4	2.8	0.4	2.5	0.5	1.6	0.2	1.7	0.3	1.8	0.1	..
D-10.....	2.5	0.4	2.3	0.3	2.2	0.4	2.8	0.4	2.2	0.4	1.7	0.2	1.7	0.3	1.8	0.1	..
D-11.....	2.6	0.4	2.4	0.3	2.2	0.4	2.4	0.3	2.2	0.4	1.4	0.3	1.5	0.1	1.8	0.4	1.7	0.1	..
D-12.....	2.3	0.3	2.5	0.3	2.3	0.3	2.3	0.3	2.1	0.3	1.8	0.3	1.5	0.2	1.9	0.5	1.9	0.1	..
L-1.....	2.4	0.4	2.3	0.3	2.1	0.3	2.2	0.3	2.3	0.4	1.8	0.4	2.1	0.4	1.9	0.5	1.9	0.3	..
L-2.....	2.4	0.4	2.3	0.3	2.1	0.3	2.0	0.3	2.1	0.3	1.8	0.4	2.1	0.4	1.9	0.5	1.8	0.3	..
L-3.....	2.2	0.4	2.5	0.3	2.2	0.3	2.2	0.3	2.2	0.6	2.0	0.4	2.5	0.6	1.9	0.5	1.8	0.3	..
L-4.....	2.2	0.6	2.8	0.4	2.5	0.4	2.4	0.4	1.9	0.6	2.1	0.4	2.5	0.6	2.1	1.9	0.3	..
L-5.....	2.5	0.5	3.0	0.2	2.3	0.4	3.0	0.5	2.5	0.3	2.9	0.7	2.5	..	2.5
Comment....	Polydactylism	Defect in isthmus between inferior and superior articular facets of L-5; congenital dislocation of hip	Spina bifida occulta dysechondroplasia	Spina bifida occulta of L-5;	Spina bifida occulta of C-7; Sprengel's deformity	Bilateral rudimentary cervical ribs of C-7	Bilateral rudimentary cervical ribs of C-7	Bilateral rudimentary cervical ribs of C-7	Bilateral rudimentary cervical ribs of C-7	Bilateral rudimentary cervical ribs of C-7	Bilateral rudimentary cervical ribs of C-7	Bilateral rudimentary cervical ribs of C-7	Bilateral rudimentary cervical ribs of C-7	Bilateral rudimentary cervical ribs of C-7	Bilateral rudimentary cervical ribs of C-7	Bilateral rudimentary cervical ribs of C-7	Bilateral rudimentary cervical ribs of C-7	Bilateral rudimentary cervical ribs of C-7
Carc.....	25	11 Years	20	25 Years	27	23	12 Years	10 Years	20	5 Years	13 Months	5 Years	32	33	5 Years	34	35	6 Years	36	37	10 Years
Age.....	Vert.	Disk	Vert.	Disk	Vert.	Disk	Vert.	Disk	Vert.	Disk	Vert.	Disk	Vert.	Disk	Vert.	Disk	Vert.	Disk	Vert.	Disk	Vert.
C-2.....
C-3.....
C-4.....
C-5.....
C-6.....	4.0	0.1	3.7	0.7	2.5	0.5	2.5	0.6	2.0	0.5	1.5	0.6	3.1	0.4	4.7	3.8	0.3	..
C-7.....	3.3	0.1	2.8	0.5	2.3	0.5	2.1	0.5	3.2	0.5	1.7	0.7	3.5	0.4	4.7	2.5	0.3	..
D-1.....	2.5	0.3	2.5	0.4	2.0	0.3	2.3	0.4	3.3	0.4	2.7	0.4	3.1	..	4.0	2.8	0.3	..
D-2.....	2.3	0.3	2.0	0.3	2.1	0.3	2.1	0.4	3.1	0.3	2.5	0.4	1.9	..	3.5	0.4	2.9	0.3	..
D-3.....	1.8	0.1	1.4	0.2	1.8	0.1	1.7	0.4	2.0	0.3	2.3	0.3	1.5	..	2.6	0.3	2.5	0.3	..
D-4.....	1.5	0.1	1.3	0.1	1.6	0.1	1.4	0.3	1.9	0.3	2.3	0.3	1.4	..	2.3	0.3	2.6	0.4	..
D-5.....	1.7	0.2	1.4	0.2	1.4	0.3	1.4	0.3	1.7	0.3	2.2	0.3	1.4	..	2.0	0.4	1.8	0.3	..
D-6.....	1.8	0.2	1.3	0.3	1.6	0.3	1.3	0.3	1.5	0.3	1.5	0.2	1.4	..	1.7	0.3	1.8	0.2	..
D-7.....	1.8	0.2	1.3	0.3	1.6	0.3	1.3	0.3	1.6	0.3	1.5	0.2	1.4	..	1.5	0.2	1.4	0.3	..
D-8.....	1.6	0.2	1.4	0.3	1.5	0.3	1.4	0.3	1.5	0.3	1.5	0.2	1.6	0.2	1.6	0.3	..
D-9.....	1.6	0.2	1.4	0.3	1.5	0.3	1.4	0.3	1.5	0.3	1.5	0.2	1.5	0.2	1.7	0.3	..
D-10.....	1.5	0.3	1.7	0.3	..
D-11.....	1.6	0.3	1.8	0.4	..
D-12.....	1.4	0.2	1.8	0.4	..
L-1.....	1.4	0.3	1.8	0.4	..
L-2.....	1.4	0.3	1.8	0.4	..
L-3.....	1.4	0.3	1.8	0.4	..
L-4.....	1.6	0.3	2.0	0.5	..
L-5.....	1.6	0.3	2.2	0.4	..
Comment	Bilateral rudimentary cervical ribs of C-7	Bilateral rudimentary cervical ribs of C-7	Bilateral rudimentary cervical ribs of C-7	Bilateral rudimentary cervical ribs of C-7	Bilateral rudimentary cervical ribs of C-7	Bilateral rudimentary cervical ribs of C-7	Bilateral rudimentary cervical ribs of C-7	Bilateral rudimentary cervical ribs of C-7	Bilateral rudimentary cervical ribs of C-7	Bilateral rudimentary cervical ribs of C-7	Bilateral rudimentary cervical ribs of C-7	Bilateral rudimentary cervical ribs of C-7	Bilateral rudimentary cervical ribs of C-7	Bilateral rudimentary cervical ribs of C-7	Bilateral rudimentary cervical ribs of C-7	Bilateral rudimentary cervical ribs of C-7	Bilateral rudimentary cervical ribs of C-7	Bilateral rudimentary cervical ribs of C-7	Bilateral rudimentary cervical ribs of C-7	Bilateral rudimentary cervical ribs of C-7	Bilateral rudimentary cervical ribs of C-7

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Measurements on the roentgenographic films revealed that the ratios of the transverse diameters to the vertical diameters of the lumbar vertebrae were higher than the normal values. It is therefore evident that the fourth and fifth lumbar vertebrae were definitely disproportioned, while the intervertebral disks were within normal range. (Compare table 5 with table 2.)

CASE 2.—E. S., a white boy 5 years of age, had been in the service of Dr. Leo Mayer for a tuberculous infection of the hip. The roentgenographic picture shown here was made incidentally, and has no relationship to the patient's complaint.

The anteroposterior roentgenographic view (fig. 2) showed that the fourth and fifth lumbar vertebrae were increased in their transverse diameters, while their vertical diameters were markedly diminished. The intervertebral disk below

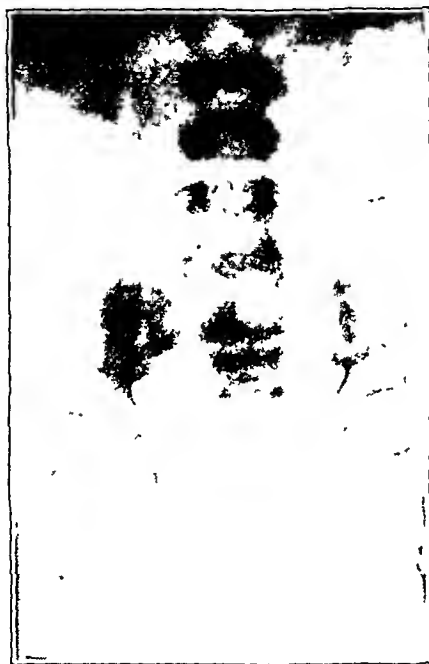


Fig. 2 (case 2).—Platyspondyly, type 1. The transverse diameters of the fourth and fifth lumbar vertebrae are increased, while their vertical diameters are diminished. The height of the fourth intervertebral disk is greater than normal. Compare with figure 3.

the fourth lumbar vertebra showed a corresponding increase in its vertical diameter. The extent of this disproportion is shown in table 5, which is to be compared with the normal values in tables 2 and 4.

Figure 3, an anteroposterior roentgenogram of a 5 year old child demonstrates visually the appearance of the fourth and fifth lumbar vertebrae and their subjacent disks under normal conditions.

CASE 3.—M. S., a 5 year old boy, was admitted to the Hospital for Joint Diseases because of acute osteomyelitis of the upper end of the femur.

The anteroposterior roentgenogram (fig. 4) revealed that the fifth lumbar vertebra was diminished in height and increased in width, while the subjacent



Fig. 3.—Visual demonstration of the normal proportions of vertebral bodies and intervertebral disks in a 5 year old child for comparison with figures 2, 4 and 5.



Fig. 4 (case 3).—Platyspondyly, type 1. The transverse diameter of the fifth lumbar vertebra is increased, and its vertical diameter is diminished. The subjacent intervertebral disk is abnormally high. Compare with figure 3.

intervertebral disk showed a corresponding increase in its vertical diameter. The upper sacral segments presented spina bifida occulta. Table 5 shows the increased ratios of the vertebrae and their intervertebral disks. A comparison of the spine in figure 4 with the normal spine shown in figure 3 will definitely establish the disproportion noted in this case.

CASE 4.—G. H., a 6 year old white boy, was admitted to the outpatient department of the Hospital for Joint Diseases because of pain in the region of the left hip joint.

Physical examination gave negative results, save for a slight limitation of internal rotation of the left thigh.



Fig. 5 (case 4).—Platyspondyly, type 1. The fifth lumbar vertebra is widened transversely and narrowed vertically. The intervertebral disks above and below are increased in their vertical diameters. Compare with figure 3.

Roentgenographic examination (fig. 5) revealed an irregularity and rarefaction at the left ischiopubic juncture. As an incidental finding it was noted that the fifth lumbar vertebra was widened transversely and narrowed vertically. The intervertebral disks above and below this segment were increased in their vertical diameters (Compare table 5 with tables 2 and 4).

CASE 5.—D. O'B., a 12 year old white girl, was admitted to the service of Dr. Samuel Kleinberg, at the Hospital for Joint Diseases, because of a slipping of the epiphysis of the upper part of the right femur and Legg-Perthes' disease of the left hip. There was no history or physical findings referable to the back.

The following findings were discovered incidentally on roentgenographic examination (fig. 6): The fifth lumbar vertebra was markedly widened trans-

versely and narrowed vertically. The intervertebral disk between the fifth lumbar segment and the sacrum was increased in its vertical dimension. (Compare table 5 with tables 2 and 4.) It was also noted that the posterior arch was not fused. The same was true of the first sacral segment.

Comment.—Cases 1 to 5, inclusive, are instances of platyspondyly of type 1 described by Putti. In all of them the roentgenographic appearances were typical; that is, there was an increase in the transverse diameters and a decrease in the vertical diameters of the lower lumbar vertebrae, most commonly the fourth and fifth. This was accom-



Fig. 6 (case 5).—Platyspondyly, type 1. The fifth lumbar vertebra is markedly widened transversely and narrowed vertically. The subjacent disk is increased in its vertical diameter.

panied in some of the instances by an increase in the vertical diameters of the intervertebral disks. These changes resulted in increased ratios, which are shown in table 5. A comparison of these abnormal ratios with the normal values shown in tables 2 and 4 reveals the extent of these variations, which were greatest in case 4. In this instance the ratios for the fourth and fifth lumbar vertebrae are 3.3 and 3.4, while the normal values for the same age group are only 1.9 and 1.9,

respectively. A relative increase in the ratios of their subjacent intervertebral disks is also present, 0.7 and 0.7, which are to be compared with the normal values, 0.5 and 0.4.

Figure 3, a normal roentgenogram of a 5 year old child, is presented to give a visual comparison between the type of spine under discussion and the normal spine.

It is also to be noted that in three of these cases there were other evidences of the congenital anomalies—spina bifida occulta of one or more vertebrae. Clinically, the patients presented asymptomatic pictures.

CASES OF TYPE 2

CASE 6.—F. DeJ., a 5 year old girl, was admitted to the first orthopedic division of the Hospital for the Ruptured and Crippled on March 11, 1927, because it had been noted that ever since birth she had been unable to turn her head. Her chin had been getting progressively closer to the chest, which was becoming more and more prominent. She had, in addition, occasional pains in the back and limbs. Notwithstanding all the deficiencies that the child had, she had been very active.

Physical examination revealed that the child was in good general condition and presented a typical appearance of Pott's disease, as evidenced by the angular curve in the upper part of the dorsal region and shortened trunk. The chin was habitually depressed on the chest.

The roentgenographic examination revealed a congenital malformation of the spine and ribs, the details of which were difficult to interpret. The anteroposterior view (fig. 7 *A*) revealed that in the lower part of the cervical region the segments were abnormally widened and thinned. In the upper part of the dorsal region there was a group of ill defined segments which were wedge shaped and partially fused into one mass. The lower dorsal and the first lumbar segments presented clear instances of somatoschisis and spina bifida. All of these segments, especially the first lumbar and lower cervical, were diminished in their vertical diameters and increased in their transverse diameters. The intervertebral disks, although not widened, dipped into the hiatuses formed by the hemivertebrae. The fifth lumbar segment was definitely widened transversely and narrowed in its vertical diameter. The sacral segments presented spina bifida anomalies. In addition, it was noted that there were apparently only ten dorsal segments. The ribs presented extensive anomalies of morphology and number. The lateral view (fig. 7 *B*) showed an irregular fusion of the upper dorsal segment. The tenth dorsal segment was markedly narrowed in its vertical diameter. There was also a failure of fusion of the centra with the posterior arches in the mid-dorsal region. The vertical diameters of the intervertebral disks were markedly irregular. The fifth lumbar vertebra was narrowed in its vertical diameter, and its adjoining disks were correspondingly increased in height.

Measurements of the various diameters to obtain the necessary ratios were not made because of the inaccuracies that would result from the marked irregularities in shape and wedging of the vertebral segments. The roentgenographic appearances are, however, so definite that one can readily appreciate the generalized increase in the ratios of the transverse to the vertical diameters of the vertebrae and the increased height of some of the intervertebral disks.

CASE 7.—S. G., a boy aged 10 months, was seen in the outpatient department of the Hospital for Joint Diseases because of a congenital torticollis on the right side.

Roentgenographic study (fig. 8) revealed that the cervical region and the three upper dorsal vertebrae were markedly thinned in their vertical diameters and widened transversely. The fifth, sixth and seventh cervical segments presented somatoschisis with an overlapping of the lateral halves of the vertebral bodies. The third and fourth cervical and the first, second and third dorsal vertebrae, although widened, presented no defects of fusion. The intervertebral disks in the entire region were proportionately increased in their vertical diameters. In addition, there was a cervical rib on the right side.



Fig. 7 (case 6).—Platyspondyly, type 2. In *A*, multiple congenital anomalies are pictured. The cervical vertebral segments are abnormally widened and thinned. In the upper dorsal regions there are a group of ill defined, wedge-shaped segments partially fused into one mass. The lower dorsal and first lumbar segments present somatoschisis, spina bifida, increased transverse diameters and diminished vertical diameters. The fifth lumbar segment is definitely widened transversely and narrowed vertically. In *B* the tenth dorsal segment is markedly thinned in its vertical axis. There is a failure of fusion of the centra with the posterior arches in the mid-dorsal region. The fifth lumbar segment is narrowed vertically.

Measurements revealed a marked increase in the ratios of the transverse to the vertical diameters of the vertebrae, as is shown by table 5, in comparison with the normal values in table 2. Corresponding measurements showed the increase in the vertical diameters of the adjoining intervertebral disks (tables 4 and 5).

CASE 8.—P. A., a white boy aged 14, was admitted to the outpatient department of the Hospital for Joint Diseases because of a congenital right cervical scoliosis.

The roentgenogram (fig. 9) revealed extensive congenital changes in the cervicodorsal region in addition to the deviation of the spine to the right. The vertebrae of the lower part of the cervical and the upper part of the dorsal region were enlarged transversely and thinned vertically, the sixth and seventh cervical and the first dorsal vertebrae being most markedly affected. Along the midline of the bodies of these vertebrae there were apices on their superior and inferior surfaces. The fourth cervical vertebra was approximately normal in width and height. In the upper part of the dorsal region several of the vertebral segments were fused into a wedge-shaped mass. (See table 5 for ratios of measurements.)



Fig. 8 (case 7).—Platyspondyly, type 2. The vertebral segments of the cervical and upper dorsal region are markedly widened transversely and thinned vertically. There is somatoschisis with overlapping of the lateral halves of the fifth, sixth and seventh cervical vertebrae. The intervertebral disks are disproportionately increased in their vertical diameters. See table 5 and compare with tables 2 and 4.

CASE 9.—The history and results of the physical examination of the patient (J. M.) were not available. A roentgenogram (fig. 10) revealed extensive platyspondyly involving the cervical and the upper part of the dorsal region. There was in addition, a hemivertebra between the sixth and the seventh cervical segments, and Sprengel's deformity bilaterally. Table 5 shows the disproportion of the transverse to the vertical diameters, expressed in numerical ratios. These values are to be compared with the normal ratios in table 2.

CASE 10.—No record of this case is available save for the roentgenograms (fig. 11), which showed an extensive narrowing of the vertical diameters and widening of the transverse diameters, most marked in the cervical region. This

disproportion was also evident in the dorsal region but to a lesser degree. Spina bifida occulta of the sixth, seventh and eighth dorsal segments was also noted. The tenth dorsal vertebra presented somatoschisis. In addition, there were cervical ribs bilaterally, while the seventh rib was markedly thinned. (Compare table 5 with the normal in table 2).

CASE 11.—M. B., a white youth aged 18, was admitted to the outpatient department of the Hospital for Joint Diseases complaining of a curvature of the spine of five years' duration. He gave no history of pain or injury to his back.



Fig. 9 (case 8).—Platyspondyly, type 2. The lower cervical and first dorsal segments are enlarged transversely and narrowed vertically. Note the apices on the superior and inferior surfaces of these vertebrae.

Clinical examination gave essentially negative results save for the local findings. There was kyphosis at the level of the upper part of the lumbar region, with a loss of the normal lumbar hollow. All motions with the exception of that at the lumbosacral articulation were obliterated. No tenderness could be elicited.

Roentgenographic examination revealed (fig. 12 *A*) a gradual increase of the transverse diameters of the vertebral segments from above downward, reaching

its maximum at the fifth lumbar vertebra. The fourth and more so the fifth segment were narrowed vertically. The intervertebral disk between the fourth and the fifth lumbar vertebra was considerably greater in its vertical diameter than those above it. (Compare table 5 with table 2.) The upper sacral segment presented a failure of fusion of its posterior arch. A lateral roentgenographic view of the spine revealed (fig. 12 *B*) bony fusion of the anterior halves of all of the vertebrae from the twelfth dorsal vertebra down to and including the fourth lumbar vertebra, with obliteration of the anterior halves of the intervertebral spaces. There were irregularities of the outlines and calcification of the upper aspect of the fourth lumbar and the anterior portions of the superior and inferior surfaces of the lower dorsal vertebrae. The latter changes were suggestive of herniations of the nucleus pulposus.

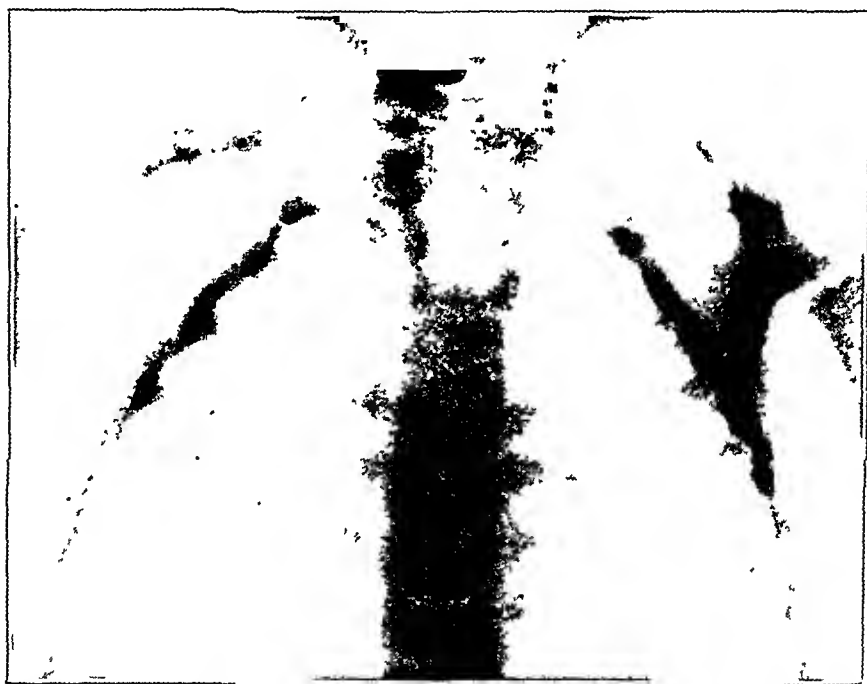


Fig. 10 (case 9).—Platyspondyly, type 2. The transverse diameters of the cervical and upper dorsal regions are increased and the vertical diameters are decreased. Note the hemivertebra between the sixth and the seventh cervical vertebra and Sprengel's anomaly bilaterally.

CASE 12.—M. C., a 5 year old girl, was admitted to the service of Dr. Finkelstein at the Hospital for Joint Diseases because of torticollis, said to be of six months' duration, resulting from mumps.

Roentgenographic examination revealed (fig. 13) an increase in the transverse diameters and a diminution in the vertical diameters of all of the cervical vertebrae. There was an associated increase of the vertical diameters of the adjacent intervertebral disks. (Compare table 5 with tables 2 and 4.) The fifth cervical body consisted of two wedges with their apexes toward the center and presented a definite somatoschisis. The transverse processes of the seventh cervical vertebra were somewhat enlarged. In view of all of these congenital anomalies the torticollis

lis may have been congenital in origin rather than acquired, for the deformity may have passed unnoticed, and the mumps may have merely focused the parents' attention on this distortion.

Comment.—Cases 6 to 12, inclusive, are instances of type 2 of platyspondyly described by Lance. This is the group of cases that are



Fig. 11 (case 10).—Platyspondyly, type 2. The vertical diameters of the cervical region are extensively narrowed and the transverse diameters are widened. There is a less evident disproportion in the dorsal region.

characterized by extensive anomalies in morphology, such as platyspondyly, wedge-shaped vertebrae, hemivertebrae, a defect in the isthmus between the superior and the inferior articular facet and the Klippel-Feil syndrome; by anomalies in numerical variations such as

occipitalization of the first cervical vertebra, dorsalization of the seventh cervical vertebra (as expressed by the presence of cervical ribs), dorsalization of the first lumbar vertebra (presence of ribs on the first lumbar vertebra), lumbarization of the first sacral vertebra and sacralization of the fifth lumbar vertebra, and finally anomalies by suppression, such as spina bifida, somatoschisis or the failure of developments

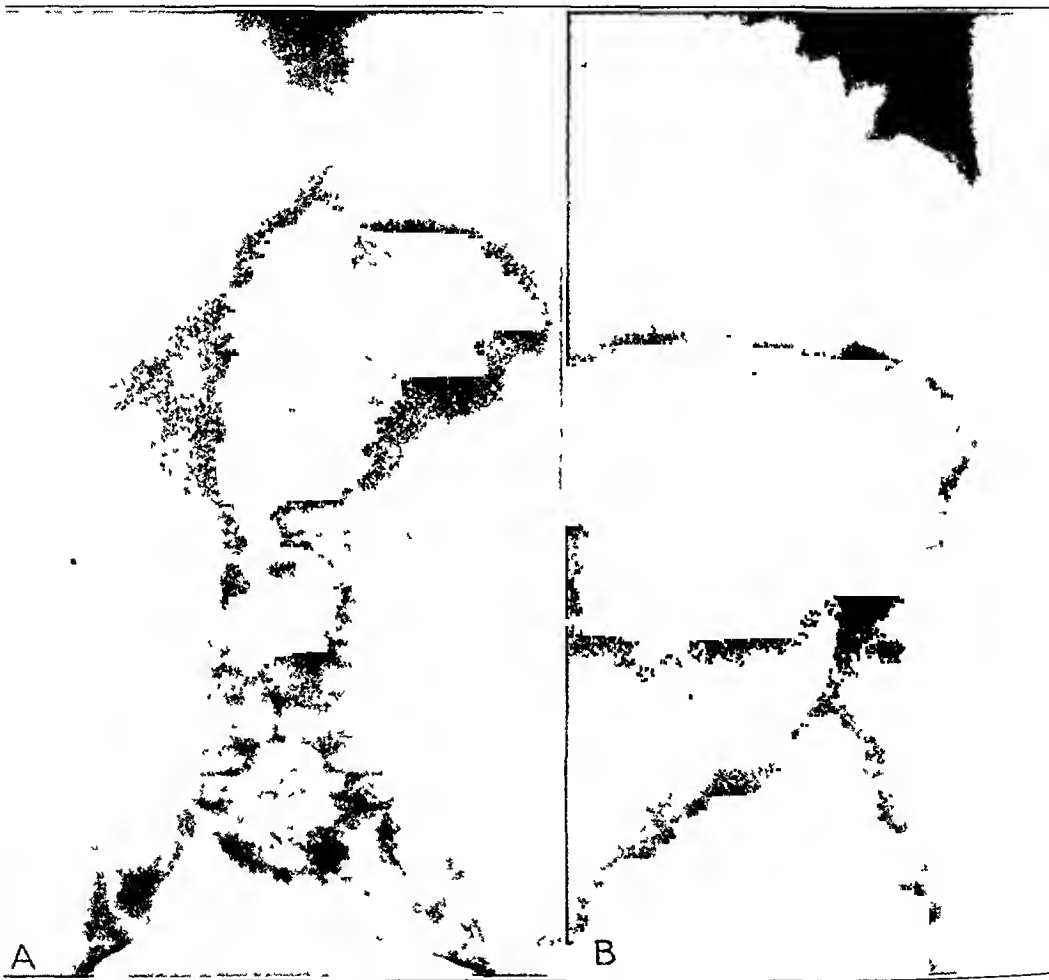


Fig. 12 (case 11).—Platyspondyly, type 2. In *A*, the transverse diameters gradually increase from above downward, the maximum size being at the fifth lumbar vertebra. The fourth and especially the fifth segments are narrowed vertically. The fourth disk is increased in height. In *B*, the anterior halves of vertebral bodies are fused with obliteration of the vertebral disks

of ossification centers. In the cases here described the platyspondylitic changes noted were associated, depending on the instance, by one or more of the foregoing variations. All of these variations occur at approximately the same period of embryologic development. The

platyspondylitic deformities are of little significance when contrasted with the other extensive congenital anomalies. Nevertheless, they are of theoretical importance in the visualization of the development of the various groups of platyspondyly. Clinically, the symptoms, if any are present, are due to the associated changes in the bony or soft tissue.

CASES OF TYPE 3. GENERALIZED FORM

CASE 13.—S. C., a 3½ year old girl, American born, of Jewish extraction, was admitted to the pediatric service of Dr. Sobel at the Hospital for Joint Diseases because of retarded development. The child apparently had a normal birth, and



Fig. 13 (case 12).—Platyspondyly, type 2. The transverse diameters are increased and the vertical diameters are diminished throughout the cervical region. There is an associated increase in thickness of the disks and somatoschisis of the fifth cervical segment.

no untoward symptoms were noted until she was 5½ months of age, when she began to cry frequently and have frequent sweating of the head. Her skin began to take a yellowish hue, and she became subject to fainting attacks, which recurred up to several months before her admission to the hospital. Occasionally there occurred a sudden pallor of the finger tips, which would disappear in a few minutes. About a month previous to admission to the hospital, treatment with cod liver oil and thyroid was instituted, and as a result the symptoms improved.

At 3 months of age the patient held her head up; at $2\frac{1}{2}$ years of age she sat up, and at 3 years and 4 months of age she was able to stand with support. Her first teeth appeared at the twenty-second month, and on admission she did not either walk or talk, while her tongue lolled and her mouth drooled.

Physical examination revealed a dull child. She held her head weakly, and in the sitting posture (fig. 14 *A*) presented a marked curve of weakness, bracing herself with one or both hands. She could stand only when her hands were held and in doing so presented evidences of weakness, as indicated by dependence on the supporting hands, hyperextended back, flexed hips and hyperextended knees (fig. 14 *B*). She was unable to walk.

Her facies was typically myxedematous; the eyes were narrow and widely spread; the tongue lolled, and the mouth drooled. The skin was dry and cold.



Fig. 14 (case 13).—Platyspondyly, type 3, generalized form. In *A*, a marked curve due to weakness of the back is pictured. Note the bracing with the left hand. In *B*, there is marked weakness of the back in the standing position. Note the dependence on the supporting hands of the attendant, hyperextended back, flexed hips and hyperextended knees. The patient was unable to stand alone or walk at $3\frac{1}{2}$ years of age.

The hair was coarse and sparse, while the scalp presented small dry yellowish scales. The eyelids were puffy, and the eyes presented an internal strabismus and fine rotatory nystagmus bilaterally. The teeth were small, widely separated and poorly developed. The pharynx was narrow and the palate had a high arch. The abdomen presented a large umbilical hernia. The back was symmetrical, and the spine was in the midline. There were no lateral deviations, and the normal antero-posterior curves were not developed, while the long posterior curve of infancy was still persistent. The spine was abnormally flexible in all directions.

The anteroposterior roentgenogram showed (fig. 15) a mild total curvature of the spine to the left. All of the vertebrae were definitely thinned in their vertical diameters and widened in their transverse diameters. This was most marked in the cervical region. The superior and inferior borders of each of these vertebrae presented a concave contour, with the apex of the concavities approximating each other in the center. Beginning with the first dorsal segment and extending down to and including the eleventh dorsal segment there was spina

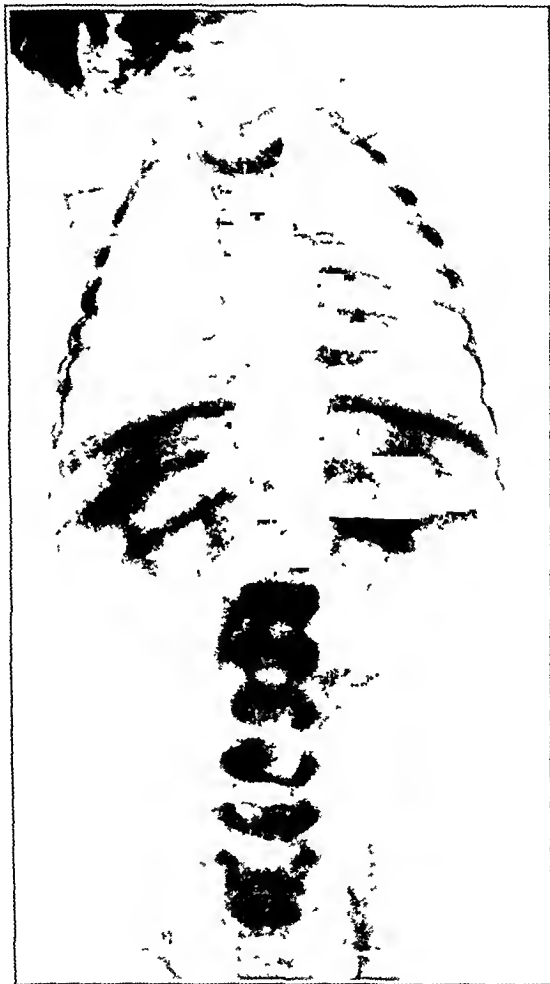


Fig. 15 (case 13).—Most characteristic generalized platyspondyly. There is widening of the transverse and diminution of the vertical diameters throughout the spine, especially in the cervical region. The superior and inferior surfaces present concavities, the apexes of which approximate each other in the midline, indicating the plane of incomplete fusion of the lateral halves of the vertebra in the membranous stage of development. The intervertebral disks are disproportionately enlarged vertically. Compare with figure 17.

bifida occulta, as was evidenced by the failure of fusion of the posterior arches. In the center of each vertebra there were two perforations, most marked in the lumbodorsal and in the upper part of the lumbar regions. These were evidently the

points of entry of the blood vessels to these segments. The intervertebral spaces were abnormally enlarged in their vertical diameters. Their superior and inferior borders were convex and corresponded with the concavities in the vertebral bodies.

The lateral roentgenogram (fig. 16) showed a total posterior curve with its apex at the second lumbar vertebra. There were marked irregularities in the anterior margins of all of the spinal segments, most marked in the midlumbar region. There were incisurae in these borders corresponding to the perforations noted in the anteroposterior view. The anteroposterior dimensions of the lumbar vertebrae varied considerably.



Fig. 16 (case 13).—There is absence of the normal anteroposterior curves. The intervertebral disks are disproportionately high. Note the incisurae, the points of entrance of intersegmental arteries indicating the plane of fusion of the caudal and cranial halves of adjoining sclerotomes to form the primitive vertebra in the membranous stage of development.

Roentgenographic examinations of the extremities showed little save for transverse lines of calcification in the metaphyses of the lower part of the femur and the upper part of the tibia and slight thickening of the cortices. The epiphysal plates of the lower part of the tibia instead of being transverse were irregular, in that the one on the left side ran obliquely upward and inward, while that on the right side ran obliquely inward and downward and then upward and inward. The carpi presented only two small centers of ossification, while the tarsi presented but four centers of ossification.

Measurements revealed that the ratios of the transverse to the vertical diameters of the various vertebrae showed a marked increase, ranging up to 7.0 for the seventh cervical vertebra, whereas the average normal for this age is only 2.3. The lowest ratio was 2.2 for third and fourth lumbar vertebrae, in contrast to the normal, 1.9. (Compare table 5 with table 2.) Corresponding measurements revealed a marked increase in the ratios of the vertical diameter of the intervertebral disks to the vertical diameters of the vertebrae. These varied from a maximum of 1.5 for the fourth cervical vertebra to 0.3 for the twelfth dorsal vertebra, the latter being the only figure within normal range. (Compare table 5 with table 4.)



Fig. 17.—A roentgenogram of a 3½ year old child showing the normal relationship between the transverse and the vertical diameters of the vertebral segments and their relationship to the height of the subjacent disks. Compare with figure 16.

Figure 17, a roentgenogram of a 3½ year old child, shows the normal relationship between the transverse and the vertical diameters of the various vertebrae. It also demonstrates graphically the normal relationship of the height of the intervertebral disks to the height of the superjacent vertebra.

CASE 14.—R. M., a 20 month old white boy, was admitted to the pediatric service of Dr. Sobel at the Hospital for Joint Diseases because of severe anemia and symptoms referable to the gastro-intestinal tract secondary to chronic lead poisoning.

Physical examination gave essentially negative results, save for evidences of anemia and poor nourishment. Examination of the blood revealed severe secondary anemia.

The anteroposterior roentgenogram of the spine (fig. 18 *A*) showed that the cervical and the first dorsal vertebrae were wider transversally than those in the upper third of the dorsal region. From this area down to and including the fifth lumbar vertebra there was a progressive widening of the vertebral bodies, reaching its maximum in the fifth lumbar segment. The normal ratio of height to width

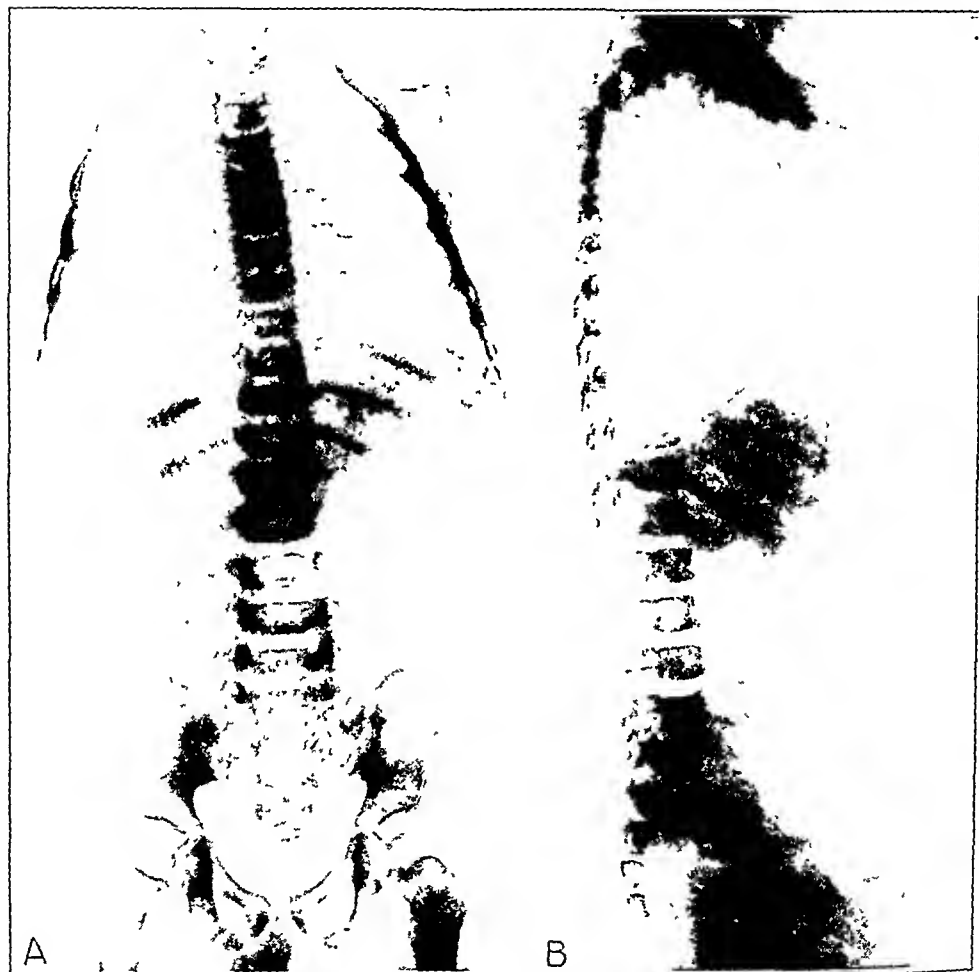


Fig. 18 (case 14).—Platyspondyly type 3, generalized form. In *A*, the defect is most marked in the lower lumbar region. In *B*, the vertical diameters of the intervertebral disks are increased, especially in the lower lumbar region.

of the bodies became increasingly disturbed from above downward, reaching its most marked disproportion in the fifth lumbar segment. Some of the vertebrae showed, mildly, the characteristic concavities on the superior and inferior surfaces. The vertical diameter of the intervertebral disks also became progressively increased toward the base of the spine. This was more clearly demonstrated in the lateral view (fig. 18 *B*).

Measurements resulted in ratios for the vertebral bodies that were higher than normal, especially for the lumbar region. The entire spine was, however, involved. The ratios for the intervertebral disks showed but a slight deviation from the normal. (Compare table 5 with tables 2 and 4).

CASE 15.—K. K., a 2 year old Negress, was admitted to the service of Dr. Kleinberg at the Hospital for Joint Diseases because of polydactylism of both hands and feet.

The results of the physical examination were essentially negative, save for the bilateral supernumerary fingers and toes.

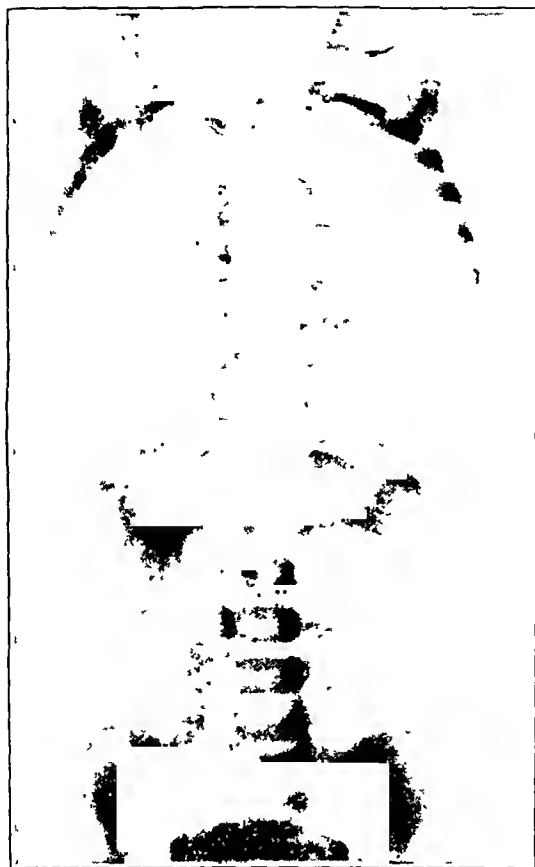


Fig. 19 (case 15).—Generalized platyspondyly, most marked in the upper and lower ends of the spine. Note the increased transverse and disproportionately small vertical diameters of the vertebral segments. The height of the intervertebral disks is increased.

A roentgenographic study was made in search of a possible platyspondyly (fig. 19). Save for the mid-dorsal region, there was a tapering increase, extending caudad and cephalad of the transverse diameters, and a decrease in the vertical diameters of all of the vertebral segments. The vertebral segments at the upper and the lower end of the spine were most involved. The foregoing changes were accompanied by increased thickness of the intervertebral disks.

Measurements revealed ratios that were more graphic in the demonstration of the disproportion between the transverse and the vertical diameters of the vertebral bodies of the entire spine. (Compare table 5 with table 4.) The measurements of the intervertebral disks showed some increase in the ratios, but only in the upper portion of the spine.

CASE 16.—J. T., a 1 year old girl, was admitted to the pediatric service of Dr. Sobel for observation for a possible tuberculous lesion of the lungs and secondary anemia. There was no history or physical findings referable to the spine.



Fig. 20 (case 16).—Generalized platyspondyly, most marked in cervical and lower lumbar regions.

Roentgenographic examination revealed (fig. 20) that the transverse diameters of the entire spine but more especially in the cervical region were markedly increased. The heights of these vertebrae were decreased, while those of the intervertebral disks were increased. (Compare table 5 with tables 2 and 4.)

CASE 17.—L. M., an 18 month old white girl, was admitted to the service of Dr. Samuel Kleinberg at the Hospital for Joint Diseases because of unilateral congenital dislocation of the hip. Roentgenograms were made of the entire spine with the idea that there might possibly be additional congenital anomalies in the form of platyspondyly. Generalized platyspondyly, type 3, and a congenital defect in the isthmus between the superior and the inferior articular facet of the fifth

lumbar vertebra were found. The latter anomaly was recently reported by Dr. Kleinberg in an article on prespondylolisthesis as occurring in the youngest patient whose case is on record.

The immediate interest in this case was aroused by a roentgenogram (fig. 21), which revealed a widening of the transverse and a diminution of the vertical diameters of all vertebrae, most marked in the upper portion of the spine. The dorsal vertebrae showed, in a measure, the typical concavities of the superior and inferior surfaces. The intervertebral disks were increased in their vertical diameters, and in the dorsal region they presented the characteristic convexities on their superior and inferior surfaces. (Compare table 5 with tables 2 and 4.)



Fig. 21 (case 17).—Generalized platyspondyly. Note the typical concavities on the superior and inferior surfaces of the mid-dorsal segments.

Comment.—Cases 13 to 17, inclusive, are instances of the generalized form of platyspondyly type 3. This form is rare, for only six cases have been heretofore described. This type is the only one that may possibly give rise to clinical symptoms and findings. I have had the opportunity to examine clinically only three patients with this type (cases 13, 15 and 17). The other cases were culled from the roentgenographic files. Clinical examination in these cases would have been inconclusive, for in patients of those ages, 1 year and 20 months, any

weakness of the spine would in all probability be referred to the physiologic weakness of infancy. In case 17 the anomaly was discovered only after the hip had been reduced and immobilized in plaster of paris. Furthermore, any findings would have been inconclusive because of the patient's age and the complicating effects of the dislocation. In case 14 there were no physical findings referable to the spine. This, however, may be accounted for by the rather mild platyspondylitic anomaly. Case 13, however, was ideal, and the findings in this instance were typical and corresponded closely to those described by Lance and others. The outstanding feature was marked weakness of the back and absence of the normal anteroposterior curves.

Roentgenographically, these cases were readily recognized, as is evident by comparing the normal appearance in figure 17 with that of any of the abnormal appearances shown in figures 15, 18 *A*, 19, 20 and 21. Measurements differentiate the normal from the abnormal, as shown in tables 5, 2 and 4.

CASES OF TYPE 3, LOCALIZED FORM

CASE 18.—J. T., a 6 year old white boy, was admitted to the service of Dr. Kleinberg at the Hospital for Joint Diseases for removal of several exostoses incidental to an extensive chondrodysplasia. The patient's father and brother have similar disturbances.

The details of the physical examination are omitted as they are irrelevant to the discussion, save that a marked shortening of both upper and lower extremities with many exostoses and widening of metaphyses was noted.

The spine was normal clinically and roentgenographically, save for the incidental finding of platyspondyly of the third, fourth and fifth lumbar vertebrae, which was most marked in the fifth, as shown in figure 22. The last lumbar segment was much narrower in its vertical diameter and wider in its transverse diameter than the vertebra above it. There was also a similar disturbance in the upper part of the dorsal region but to a less marked degree. The subjacent intervertebral disk of the fifth lumbar vertebra was increased in height when compared with those above it. There was, in addition, a failure of fusion of the posterior arch of the fifth lumbar segment.

Measurements yielded the various ratios, as shown in table 5, and comparisons with the average normal values, to be found in tables 2 and 4, reveal the disturbance very distinctly.

This case demonstrates that no hard and set rules may be laid down in the classification of the various types. Because of the involvement of the lower part of the lumbar region, one may classify this as an instance of type 1. In this instance, as in several subsequent cases to be reported, there were two areas involved, that is, the upper part of the dorsal region and the lower part of the lumbar region. It is because of this multiplicity of the lesion that it has been classified as type 3, localized form.

CASE 19.—J. F., a 6½ year old white boy, was admitted to the outpatient department of the Hospital for Joint Diseases with the chief complaint of round shoulders. The past history of the patient is irrelevant

Physical examination revealed that the child was in good general condition. It was noted that the neck was abnormally short and wide and that the hair line was unusually low. The right shoulder was narrower than the left, and the right scapula was higher than the left. Rotation of the neck to the left was possible only to 35 degrees; rotation to the right was limited at 45 degrees. Flexion of the neck was only one half of the normal range, while extension and hyperextension were normal. The back was normal clinically save for a moderate increase in the posterior curve of the spine in the dorsal region.



Fig. 22 (case 18).—Platyspondyly, type 3, localized form, most marked in fifth lumbar vertebra. (See text.)

Roentgenographic examination revealed (fig. 23) that the cervical vertebrae were wider than normal. This increase in width diminished gradually caudally to the third dorsal vertebra, which was of normal size. The vertical diameters of the cervical vertebrae were irregular and less than normal. The sixth cervical segment was markedly thinned and presented concavities on its superior and inferior surfaces. There was spina bifida occulta of the seventh cervical vertebra. The second and third dorsal vertebrae were abnormally narrow in their vertical diameters, while their transverse dimensions were approximately normal. It was also noted that the right scapula was situated about 1 inch cephalad in comparison to the left.

Roentgenographic study (fig. 24) of the lumbar region showed that the third, fourth and fifth lumbar vertebrae were widened in their transverse diameters and narrowed in their vertical dimensions. There was spina bifida occulta of the first



Fig. 23 (case 19).—Localized form of platyspondyly, type 3, involving the cervical and the upper three dorsal segments. The sixth cervical segment shows an extremely marked diminution of its vertical diameter with concavities on its superior and inferior surfaces. This case presented a second focus in the lumbar region. See figure 24.

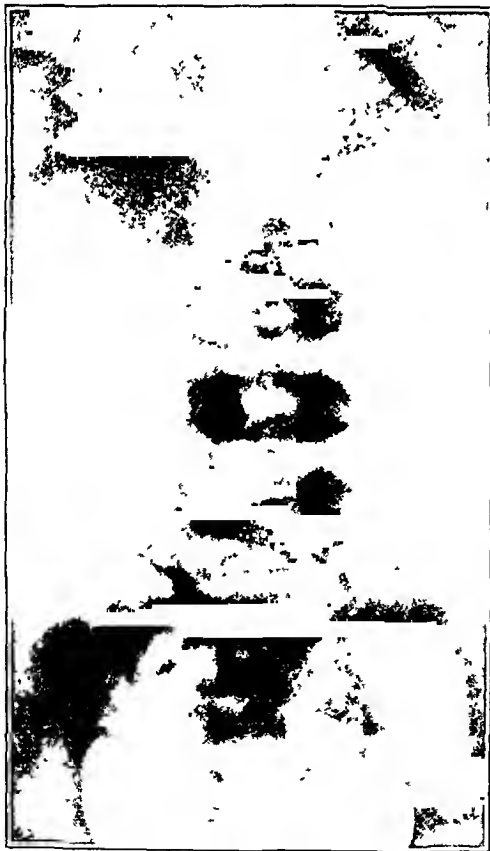


Fig. 24 (case 19).—Localized form of platyspondyly, type 3, involving the lumbar region, most marked in the fifth lumbar segment. This case presented a second focus in the cervical and upper dorsal region. See figure 23.

sacral segment. The intervertebral disks in this region were abnormally thickened. (Compare table 5 with tables 2 and 4.)

CASE 20.—P. R., a 9 year old white girl, was admitted to the service of Dr. Finkelstein at the Hospital for Joint Diseases because of a mild residual paralysis of one of the lower extremities subsequent to poliomyelitis.

As an incidental finding it was noted that in the upright position the child's posture was very poor in that there was a definite increase in the posterior curva-



Fig. 25 (case 20).—Localized form of platyspondyly, type 3, involving the lumbar region presenting a fusiform widening of the spine, most marked in the fifth lumbar segment.

ture in the dorsolumbar region and a loss of the normal lumbar hollow. In the sitting position she presented a total posterior curve. All motions of the spine were unrestricted and painless. There was no tenderness anywhere, save over the iliac crests.

Roentgenographic study (fig. 25) revealed that beginning with the first lumbar vertebra and descending downward there was a gradual increase in the transverse

diameters and a decrease in the vertical diameters of the vertebral segments, culminating in a maximum change in the fifth lumbar vertebra. This was associated with a moderate increase in the height of the intervertebral disks.

Measurements yielded increased ratios that were indicative of the disproportion between the transverse and the vertical diameters of the vertebrae and the height of the intervertebral disks, all in the lumbar region. (Compare table 5 with tables 2 and 4.)

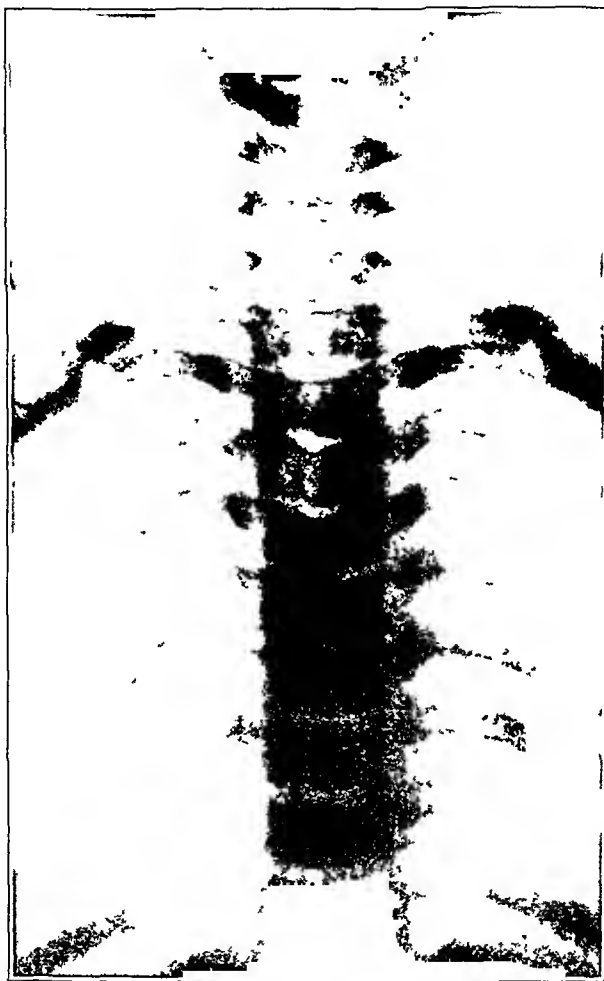


Fig. 26 (case 21).—Localized platyspondyly, type 3, of the cervical and upper dorsal segments. Note the concavities on the inferior surfaces of the cervical vertebrae and the disproportion of the various diameters.

CASE 21.—W. H., an 8 year old boy afflicted with a right spastic hemiplegia associated with a cerebral retardation, while under treatment at the Hospital for Joint Diseases sustained an injury to the back of his neck.

Physical examination revealed a deep-seated cervical adenitis.

Roentgenographic examination (fig. 26) showed that the vertebrae of the entire cervical region were wider transversely than those in the dorsal segment

The diminution in width was gradual from above downward, so that the upper dorsal vertebrae were also involved in the same process. It was also noted that the vertical diameter of the cervical vertebrae was less than normal and that the increase in height in the upper dorsal segment was gradual. Similarly, the affected vertebrae presented concavities on their superior and inferior surfaces, while the intervertebral disks were proportionately increased in height. The seventh cervical vertebra presented bilateral cervical ribs.

The ratios of the transverse diameters to the vertical diameters of the vertebrae and the ratios of the heights of the intervertebral disks to those of the adjoining vertebrae were increased beyond the normal (table 5). Comparison of these data with those shown in tables 2 and 4 bears out the visual impression that one gets on inspection of figure 26.



Fig. 27 (case 22).—Localized platyspondyly, type 3, of the cervical and upper dorsal region. Note the barrel-shaped enlargement of the cervical region, the concavities on the inferior surfaces and the convexities on the superior surfaces of the cervical segments.

CASE 22.—S. S., a 7 year old white girl, was admitted to the outpatient department of the Hospital for Joint Diseases because of poor posture.

Clinical examination gave essentially negative results, save for the presence of a hollow round back.

Roentgenographic study (fig. 27), however, revealed a barrel-shaped enlargement of the cervical region. The entire cervical region tapering down to include the upper two dorsal vertebrae was widened transversely and narrowed vertically.

The superior surfaces of these segments presented convexities, while the inferior aspects presented concavities. The intervertebral disks were correspondingly enlarged. The seventh cervical vertebra presented in addition bilateral cervical ribs which were much more distinct in the x-ray film than in the appended print. A comparison of table 5 with tables 2 and 4 shows the numerical increase in the ratios of the transverse diameters to the vertical diameters of the vertebrae and in the ratios of the heights of the intervertebral disks to the heights of the vertebrae.

CASE 23.—S. G., a 3½ year old white boy, was admitted to the outpatient department of the Hospital for Joint Diseases because of a stiff neck. One month previous to admission he fell and had a bloody nose. Three weeks later his neck became stiff, and he had a rise in temperature, with generalized aches and pains.



Fig. 28 (case 23).—Localized platyspondyly, type 3. Note the fusiform widening of the cervical region tapering downward to include the upper two dorsal segments.

Clinical examination gave negative results save for an enlargement of the cervical, submaxillary and inguinal glands.

Roentgenographic examination (fig. 28) revealed a fusiform widening of the cervical portion of the spine tapering downward to include the upper two dorsal vertebrae. The vertebral segments in this region were widened transversely and narrowed vertically. The intervertebral disks were correspondingly enlarged. The seventh cervical vertebra presented bilateral cervical ribs. Table 5 shows ratios obtained by measurements for this case. Comparison with the normal averages shown in tables 2 and 4 shows the increase above the normal.



Fig. 29 (case 24).—Localized platyspondyly, type 3, involving the cervical and first dorsal vertebrae. The inferior surfaces of the cervical vertebrae are markedly concave.



Fig. 30.—The normal appearance of the cervical and dorsal regions of an 11 year old boy. Compare with figures 29, 31 and 32.

CASE 24.—E. B., an 8 year old white girl, was admitted to the outpatient department of the Hospital for Joint Diseases. The history and the results of the physical examination were not available.

Examination of the x-ray films (fig. 29) revealed that the cervical and the first dorsal vertebrae were enlarged transversely and narrowed vertically. The inferior surfaces of the cervical vertebrae were markedly concave, while the superior surfaces were mildly convex. The intervertebral disks were correspondingly increased in their horizontal and vertical diameters and conformed with the concavities and convexities of the adjacent vertebrae. There were, in addition, bilateral rudi-



Fig. 31 (case 25).—Localized platyspondyly, type 3, of the cervical and upper dorsal vertebrae. The fifth cervical vertebra is markedly involved.

mentary cervical ribs at the seventh cervical segment. Comparison of table 5 with tables 2 and 4 shows the actual change in the relationship between the transverse and the vertical diameters of the vertebrae and the relationship between the height of the disks and that of the vertebrae.

Figure 30, an anteroposterior view of the cervicodorsal region of an 8 year old child, shows the normal relationship of the transverse to the vertical diameters of the cervical vertebrae to those of the dorsal region. This appearance is to be compared with figure 29, which shows a platyspondyly, to appreciate the normal from the abnormal.

CASE 25.—A. B., an 11 year old white boy, was admitted to the outpatient department of the Hospital for Joint Diseases with the complaint of poor posture. Two years previously he suffered from empyema.

Physical examination revealed a poorly nourished, poorly developed white boy presenting kyphosis dorsalis juvenilis.

Roentgenographic examination (fig. 31) revealed typical platyspondyly of the cervical and the upper two dorsal vertebrae. The vertebrae of the involved segment were wide transversely, tapering downward to include the second dorsal segment, and were narrowed vertically, increasing in height as the lower limit of the area was approached. The fifth cervical vertebra was most characteristic in that it presented a marked concavity on both the upper and the lower surface. The seventh cervical vertebra presented bilateral cervical ribs. The changes in the vertebral diameter expressed, numerically, are shown in table 5. (Compare these values with the normal values, as shown in tables 2 and 4.)



Fig. 32 (case 26).—Localized platyspondyly, type 3, of the cervical and the first two dorsal vertebrae.

CASE 26.—G. St. C., an 11 year old white girl, was admitted to the outpatient department of the Hospital for Joint Diseases because of a prominence of the back of the neck.

Physical examination gave negative results, save for a thickening of the base of the neck.

Roentgenographic study (fig. 32) revealed that the cervical region was abnormally enlarged transversely, tapering downward in width to include the first and second dorsal vertebrae. The vertical diameters of the vertebrae were diminished, increasing gradually as one approached downward to the second dorsal vertebra. There were, in addition, the typical concavities and convexities of the inferior and superior surfaces of the vertebrae. The intervertebral disks were but slightly

enlarged in their vertical diameters save at the midlines of the bodies where the enlargement was marked. Bilateral rudimentary cervical ribs were present at the seventh cervical vertebra. (Compare table 5 with tables 2 and 4.)

CASE 27.—I. B., a 25 year old woman, was seen and roentgenograms made to determine whether she had cervical ribs. The history and the results of the physical examinations were not available.

The x-ray film (fig. 33) revealed a generalized transverse enlargement of the cervical and first dorsal segments. The vertical diameters and the intervertebral



Fig. 33 (case 27).—Localized platyspondyly, type 3, of the cervical region.

disks were diminished. The inferior surfaces of the cervical vertebrae presented slight concavities. The transverse processes of the sixth and seventh cervical vertebrae were hypertrophied. (Compare table 5 with tables 2 and 4.)

CASE 28.—L. S., a 12 year old white girl, was admitted to the outpatient department of the Hospital for Joint Diseases. The history and the results of the physical examination were not available.

The x-ray film (fig. 34) culled from the x-ray files showed a fusiform enlargement of the entire cervical region, including the upper two dorsal segments. The width was greatest in the lower cervical area, thus suggesting a barrel-shaped enlargement. The vertical diameters of the segments were diminished, while those

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of the intervertebral disks were increased. The transverse processes of the seventh cervical vertebra were enlarged. (Compare table 5 with tables 2 and 4.)

Figure 35 is an anteroposterior view of a normal cervicodorsal region of a 13 year old child for comparison with the abnormal appearance shown in figure 34 and others.

CASE 29.—R. S., a 10 year old white girl, was treated by me several years ago at the Israel Zion Hospital for bilateral fracture of the clavicles, sustained as a result of an automobile accident. The end-result was satisfactory, and the patient had no complaint with reference to her neck.



Fig. 34 (case 28).—Localized platyspondyly, type 3. Note the barrel-shaped enlargement of the cervical region.

A recent roentgenogram showed (fig. 36) as an incidental finding a marked widening of the cervical and upper dorsal vertebrae tapering down to a normal width at the second dorsal vertebra. The vertical diameters of the vertebrae were diminished in this region. Several of the segments presented concavities on their superior and inferior surfaces. There were in addition, bilateral rudimentary cervical ribs. (Compare table 5 with tables 2 and 4.)

CASE 30.—I. P., a 5 year old girl, was admitted to the outpatient department of the Hospital for Joint Diseases because of pain and stiffness of the neck following a second injection of toxin-antitoxin for diphtheria.

Physical examination revealed that the child held its head with the chin tilted upward and to the left. The ranges of motion of the neck were normal in all directions. The base of the neck was found to be thickened. Physical therapy and support were instituted, and the patient was relieved of the torticollis.



Fig. 35—A roentgenogram of a normal cervicodorsal region of a 13 year old child, for comparison with figure 34.



Fig. 36 (case 29).—Localized platyspondyly, type 3, of the cervical and upper dorsal region. Note the bilateral cervical rudimentary ribs.

Roentgenographic examination (fig 37) revealed a fusiform widening of the cervicodorsal region with its greatest dimensions at the seventh cervical vertebra. The vertical diameters of the segments in this area were diminished, and the heights of the intervertebral spaces were increased. There were bilateral rudi-

mentary cervical ribs at the seventh cervical vertebra. (Compare table 5 with tables 2 and 4 for the relative ratios) There was, in addition, a Sprengel's deformity, in that one scapula was definitely higher than its mate on the opposite side.



Fig. 37 (case 30).—Localized platyspondyly, type 3, of the cervical region. The associated congenital anomalies are Sprengel's deformity and bilateral cervical ribs.



Fig. 38 (case 31).—Localized platyspondyly, type 3. The cervical region presents a barrel-shaped enlargement perched on the dorsal segment of the spine. The disproportion of the various diameters is marked.

CASE 31.—R. H., a 13 month old boy, was seen in the outpatient department of the Hospital for Joint Diseases because of a flexion deformity of the left

thumb, which had been noted by the mother since birth. Physical examination gave negative results from the orthopedic aspect, save for the flexion contracture of the thumb.

Roentgenographic examination (fig. 38) of the cervicodorsal region of the spine revealed a marked disproportion in the relationship of the width to the height of the cervical vertebrae. The whole appearance was that of a barrel-shaped enlargement perched on the dorsal segment of the spine. (Compare table 5 with table 2.)

CASE 32.—S. R., a 5 year old girl, was admitted to the service of Dr. Finkelstein at the Hospital for Joint Diseases because of a torticollis of five days' duration resulting from a somersault in bed. The deformity was diagnosed as an anterior subluxation of the atlas, which was relieved after several days of traction in bed.



Fig. 39 (case 32).—Localized platyspondyly, type 3, of the cervical region.

As an incidental finding of the roentgenographic study (fig. 39) a disproportional widening of the transverse diameters and a diminution of the vertical diameters of the cervical vertebrae were noted. The intervertebral disks presented an increase in their vertical diameters. (Compare table 5 with tables 2 and 4.) There were, in addition, bilateral rudimentary cervical ribs.

CASE 33.—S. R., a 5 year old girl, was admitted to the Hospital for the Ruptured and Crippled in 1924 for the treatment of a condition totally unrelated to her back. The history was unimportant, and physical examination gave negative results so far as the spine was concerned. This case was therefore included in a study of the normal ossification centers that was being made at that time. Roentgenograms were taken and were considered normal at that time.

A reexamination of these films brings to light that there is an increase of the transverse diameters and a disproportionate decrease of the vertical dia-

meters of the cervical and upper four dorsal vertebral bodies. A visual picture of this disturbance is shown in figure 40, while table 5 and a comparison of the values presented therein with the normal values shown in tables 2 and 4 give a mathematical picture of this condition.

CASE 34.—H. D., a 5 year old boy, was admitted to the service of Dr. Mayer at the Hospital for Joint Diseases because of a residual poliomyelitis affecting the right hand.

As an incidental finding, in the roentgenographic study (fig. 41) enlargement of the transverse diameters and a diminution of the vertical diameters of the lower

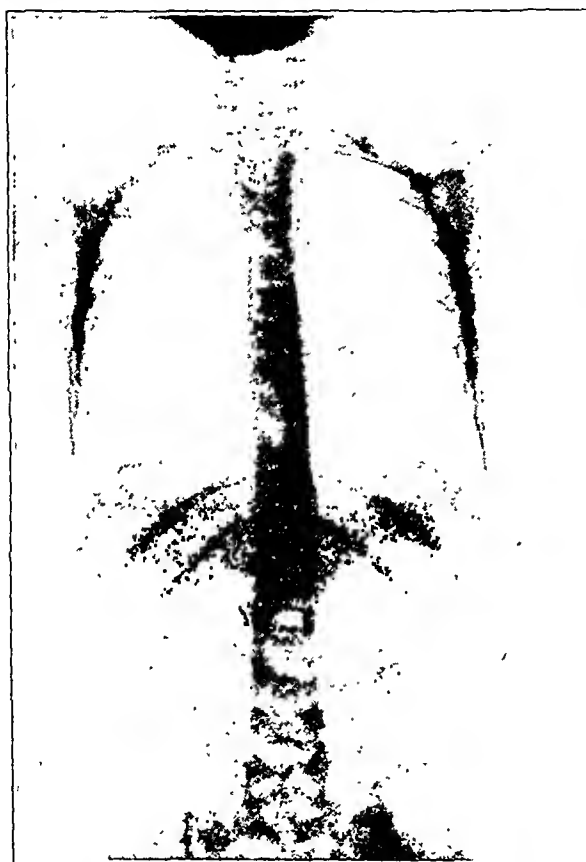


Fig. 40 (case 33).—Localized platyspondyly, type 3, of the cervical region.

cervical and upper dorsal vertebrae were noted. The intervertebral disks were markedly increased in their vertical diameters. (Compare table 5 with tables 2 and 4.)

CASE 35.—R. L., a 6 year old boy, was admitted to the service of Dr. Leo Mayer because of congenital torticollis. There was no history or physical findings referable to the patient's spine.

Roentgenographic examination (fig. 42) showed a fusiform enlargement of the cervical portion of the spine. The vertebrae were enlarged transversely and disproportionally diminished vertically. The fifth and sixth cervical vertebrae presented a failure or an incomplete fusion of the lateral masses to the centra of



Fig. 41 (case 34).—Localized platyspondyly, type 3, of the cervical region. The disproportion is marked in the upper cervical region.



Fig. 42 (case 35).—Localized platyspondyly, type 3. Note the failure or incomplete fusion of the lateral masses to the centra of the fifth and sixth cervical segments.

the vertebrae. (See table 5 for the ratios of the respective diameters.) The seventh cervical vertebra presented, in addition, rudimentary cervical ribs.

CASE 36.—I. B., a 7 year old boy, was admitted to the Hospital for the Ruptured and Crippled in 1927, for the treatment of congenital talipes. The history was unimportant, and physical examination gave negative results so far as his spine was concerned. Roentgenograms were taken at that time, for the purpose of studying the normal complementary ossification centers.

A restudy at the present time revealed (fig. 43) what was not evident at that time, namely, a disproportional increase of the transverse diameters and a lessen-



Fig. 43 (case 36).—Localized platyspondyly, type 3, of the cervical and upper two dorsal vertebrae.

ing of the vertical diameters of the cervical and upper two dorsal segments. Several of the intervertebral disks showed a disproportional increase in their vertical diameters. (Compare table 5 with tables 2 and 4.)

CASE 37.—F. K., a 10 year old boy, was admitted to the Hospital for the Ruptured and Crippled in 1924 for a condition totally unrelated to his spine. Physical examination gave negative results so far as his spine was concerned. Roentgenograms were taken to observe the normal ossification of the superior and inferior vertebral epiphyses.

A restudy at the present time revealed (fig. 44) that the transverse diameters of the vertebral bodies were disproportionally increased in comparison to the ver-

tical diameters of the same segments. This disproportion began with the first lumbar body and became increasingly greater as one progressed, caudad, reaching a maximum at the fifth lumbar vertebra (table 5). The height of the intervertebral disks were not increased. There was, in addition, a failure of fusion of the posterior arch of the first sacral segment, and in the lateral views one noted a defect in the isthmus between the superior and the inferior articular facets of the fifth lumbar vertebra.

CASE 38.—S. Z., a 3½ year old boy, was admitted to the Hospital for Joint Diseases for a condition totally unrelated to his spine. Roentgenograms were made of the spine for the purpose of obtaining a normal standard. Much to our surprise, a marked case of platyspondyly was found, as shown in figure 45. All of the cervical vertebrae showed a marked increase in the transverse diameters



Fig. 44 (case 37).—Localized platyspondyly, type 3, of the lumbar region. The disproportions of the diameters become progressively greater from above downward.

and a decrease in the vertical diameters. The first and second dorsal vertebrae showed a diminution in the height, but no increase in the width of the bodies. The intervertebral spaces were increased. There was, in addition, a rudimentary cervical rib at the seventh cervical segment.

Comment.—Cases 18 to 38, inclusive, are examples of the localized form of the third type of platyspondyly described by Lance. The most common site of involvement in these cases is in the cervical and cervico-dorsal region. The lower part of the lumbar region is the next most common area of involvement. I have not as yet noted any instance in which the other regions of the spine were affected except in the

generalized forms. In several of the cases there were two areas of localization. The great majority of the patients had associated congenital anomalies, the most frequent of which were hypertrophied transverse processes and cervical ribs. In three instances there was a unilateral or bilateral Sprengel's deformity. In another instance there was a defect in the isthmus between the superior and the inferior articular facets of the fifth lumbar vertebra. In still another instance there was a failure of fusion of the lateral masses to the centra of

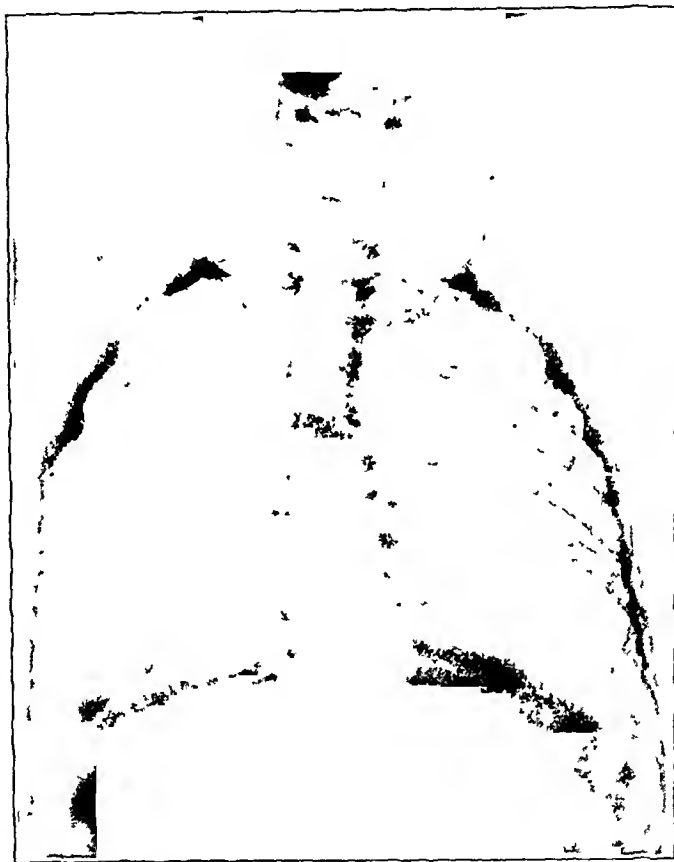


Fig. 45 (case 38).—A marked case of localized platyspondyly, type 3, of the cervical region.

two vertebrae. In addition, there were other congenital deformities, such as torticollis, talipes and a flexion deformity of a thumb. All of this serves to depict the congenital nature of this disturbance.

Clinically, the anomaly is asymptomatic, except so far as the associated condition may produce physical or symptomatic changes. Roentgenographically, the changes are very evident. This is confirmed by the ratios resulting from actual measurements on the films, as shown

in table 5, and a comparison of these with the normal values shown in tables 2 and 4. Figures 30 and 35 are views of roentgenograms of normal spines for comparison with the abnormal appearances as illustrated by the cases.

DIFFERENTIAL DIAGNOSIS

Platyspondyly is a congenital lesion of the spine in which the vertebrae in one or more segments are abnormally developed. It is usually recognized accidentally in early life, chiefly through specific changes in the roentgenographic appearance. In the anteroposterior view the vertebral bodies all seem to be increased in their transverse diameters and diminished in their vertical diameters. The superior and inferior surfaces are concave, while the intervertebral disks are biconvex, wider and higher than normally. In the lateral views the vertebrae are abnormally small in the vertical diameters and are never wedge shaped. There is practically always, except in type 3, the developmental defect of spina bifida or somatoschisis. This vertebral malformation, save in type 1, usually involves more than one spinal segment which, because of the morphologic alteration of the vertebrae, has a fusiform or truncated cone shape. The recognition of the aforementioned morphologic deviations is important in differentiating platyspondyly from other more frequent and clinically more important abnormalities, both congenital and acquired. Usually little difficulty will be encountered when an extensive portion of the spine is involved in this congenital malformation. However, should this maldevelopment affect only one or several segments of the vertebral column, the differential diagnosis may not be so apparent. The most common of the lesions from which platyspondyly has to be differentiated are: Pott's disease, compression fractures of the spine, malignant disease, vertebral epiphysitis, vertebral osteochondritis, osteoporosis, microspondyly, fetal chondrodystrophy and herniations of the nuclei pulposi.

Pott's Disease.—The usual case of Pott's disease will offer no difficulties in differential diagnosis because of the disability, the localized pain and deformity and the roentgenographic picture of rarefaction, destruction, collapse, loss of intervertebral disks and abscess formation. Occasionally, however, a case may be seen in which there is compression but no other evidence of tuberculous disease. Here, however, the vertebral body will show wedging but rarely widening in the anteroposterior roentgenogram. Moreover, there will be roentgen evidences of a destructive disease. The clinical history, the physical findings, the roentgenographic appearances and the absence of other congenital anomalies should establish the diagnosis.

These roentgenographic appearances are in sharp contradistinction to those in platyspondyly, which never show abnormalities in ossification or changes in the vertebral disks other than those of shape and size.

Vertebral Osteochondritis.—Vertebral osteochondritis develops during the first period of rapid growth of the spinal column—the first few years of life. The history reveals evidences of pain and increasing deformity. Clinically, there may be indications of tenderness along the spine. Localized deformity may be present. Roentgenographically, one or several vertebrae may be involved in that there are irregularities in ossification and vertebral outlines. There may be wedging of the vertebral segments, but neither widening in the transverse diameters nor the characteristic concavities noted on the superior and inferior vertebral surfaces in instances of platyspondyly.

Osteoporosis.—The rare forms of hunger, traumatic or senile osteoporosis of the spine may present flattening of the vertebrae but never widening. The bony texture of the bodies is porotic, while in platyspondyly it is always normal. The superior and inferior borders of the vertebral outlines may be definitely concave, but these depressions are most clearly demonstrated in the lateral views, while in platyspondyly they are seen only in the anteroposterior views. The concavities usually involve the entire superior and inferior surfaces, while in platyspondyly only the midportions are involved. In osteoporosis of the spine herniation of the nucleus pulposus is common, in contradistinction to its absence in platyspondyly. In osteoporosis there are wedging and increase of the posterior curvature of the spine. Furthermore, the absence of other congenital anomalies, the history of onset, the symptoms and the physical findings will make the differential diagnosis evident.

Microspondyly.—Microspondyly presents an aplasia of the entire vertebra. The vertical diameter as well as the transverse and sagittal diameters are lessened. This anomaly has its onset in a comparatively later stage of embryonic life, the stage of ossification. Consequently the vertebrae have already been formed before this disturbance sets in, and its only effect is a generalized diminution in size. Because of its late onset it is not associated with those anomalies of the membranous stage, such as variations in number, morphology or differentiation and associated costal maldevelopments.

Fetal Chondrodystrophy.—In this condition there is widening of the vertebral bodies associated with distinguishing irregularities in outline and ossification. The intervertebral disks are not disproportionately enlarged, nor do the vertebrae present the characteristic concavities or the presence of spina bifida or somatoschisis. Congenital anomalies arising in the membranous stage are absent. Furthermore, the general

picture of disproportion in length between the extremities and the spine, the typical saddle nose, the trident hand and the premature ossification of epiphyses everywhere and the deformities of the extremities will present no difficulties in differentiating this condition from platyspondyly.

Herniation of the Nucleus Pulposus.—This pathologic condition is most evident in the lateral views of the spine, although occasionally it can be clearly demonstrated in the anteroposterior aspects. Reactive processes on the part of the bone in the form of rarefaction or increased calcification around the herniations are usually present. Herniation of the nucleus pulposus is not a clinical entity and is therefore always a part of some other disturbance, such as osteoporosis of the spine, Kummell's disease, fractures, malignant disease or osteochondropathy.

SUMMARY

Platyspondyly, as has been shown in the preceding description and observations, is a definite congenital morphologic disturbance of the growth of the spine manifesting itself in several distinct types. Its genesis may be attributed to a failure or a delay in the fusion of the lateral halves of the vertebral anlage at its membranous stage of embryonic development. The roentgenographic changes in the vertebrae and the intervertebral disks are distinctive. They have been described in detail since they render the recognition of platyspondyly certain. Perhaps the most important aspect of this study of platyspondyly is that by establishing its essential characteristics numerous other somewhat similar but usually clinically far more important lesions of the spine may be readily differentiated.

As the ratios between the vertical diameters and the transverse diameters of normal vertebrae are fairly constant, I measured about one hundred and forty-five normal spines to establish an index. I then obtained the corresponding index in the cases of platyspondyly. A comparison of the two was convincing of the marked alterations in the lesion which is the subject of this thesis. It is believed and hoped that this phase of the work on mensuration will facilitate later reviews on platyspondyly.

Dr. Samuel Kleinberg, chief of my orthopedic service at the Hospital for Joint Diseases, and Dr. Maurice Pomeranz, director of the Roentgen Ray Laboratory of the Hospital for Joint Diseases, gave valuable advice and guidance in the study; Dr. Armitage Whitman, of the Hospital for the Ruptured and Crippled, and Dr. Leo Mayer, Dr. Harry Finkelstein and Dr. Jacob Sobel, of the Hospital for Joint Diseases, permitted me to use their material, and Dr. Leo Schwartz and Dr. Milton Wasch, of the Israel Zion Hospital, permitted me to make roentgenograms of the new-born.

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STREPTOCOCCUS HAEMOLYTICUS BACTEREMIA

A STUDY OF ONE HUNDRED AND SIXTY-EIGHT CASES

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We have had the opportunity of reviewing an unusually large number of cases of *Streptococcus haemolyticus* bacteremia occurring within a comparatively short period. In the five and one-half years with which this study is concerned there have been 168 such cases observed in the various medical and surgical departments of the Mount Sinai Hospital. This constitutes about one fifth of all cases of proved bacteremia occurring during the stated period. Furthermore, this group included a variety of infections of unusual interest and clinical significance, the recognition and proper interpretation of which were important not only for diagnosis but for prognosis and treatment.

Because of the comparatively high incidence of *Str. haemolyticus* bacteremia and the clinical importance of such infections of the blood stream, we felt that a comprehensive study of these cases would be both interesting and valuable. In this study, in a large group of consecutive cases we tried to classify the various conditions in which *Str. haemolyticus* bacteremia occurred and to determine the significance of the bacteriologic picture in each group of cases. The route of invasion into the blood stream was used for the grouping of the cases. Each group was further studied in relation to age, seasonal incidence, prognosis and the clinical picture observed. In analyzing the blood cultures we were also interested in the diagnostic and prognostic significance of the number of organisms cultivated from the blood stream.

REVIEW OF THE LITERATURE

The literature on sepsis elicited by various micro-organisms, including *Str. haemolyticus*, is fully reviewed and extensively discussed by Leschke,¹ and that of human streptococcic infections by von Lingelsheim.² As the scope of this paper will not permit a complete review of

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2. von Lingelsheim, W. V., in Kolle, W., and Wassermann, A.: *Handbuch der pathogenen Mikroorganismen*, Jena, Gustav Fisher, 1928, vol. 4, p. 789.

the literature, references are limited to papers concerning certain aspects with which we were directly interested.

In 1906 Libman³ published reports of a series of cases of *Str. haemolyticus* bacteremia in which there was first demonstrated the importance of blood cultures in the diagnosis and operative indications of thrombosis of the lateral sinus. These observations were later extended by Libman and his collaborators⁴ and corroborated by Sondern⁵ in 1911, Hays⁶ in 1912 and by others. Reports on *Str. haemolyticus* bacteremia secondary to various foci were made by Warren and Herrick⁷ in their summary of 31 cases. The mortality rate in this series was 67 per cent. The series included cases of bacteremia following scarlatinal, peripheral, otitic and pelvic infections. Erb⁸ in 1923 presented a report dealing with the mortality rate, seasonal incidence and distribution of various lesions in 350 cases of *Str. haemolyticus* infection in children. Observations concerning sepsis following erysipelas are of special interest and will be reviewed later in this paper.

The study of epidemics of milk-borne *Str. haemolyticus* infection by Theobald Smith and H. J. Brown,⁹ Rathery and Du Castle,¹⁰ Capps and Davis¹¹ and L. H. Smith¹² included a large group of cases in which the infection was of unusual virulence, with a high mortality rate and multiple metastases. There is also published a series of reports on a single case or on small groups of cases by Dunham,¹³ Miller,¹⁴ Bourges,¹⁵ Berghausen,¹⁶ Eggston¹⁷ and Ballenger.¹⁸ Neuhof, Aufses

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16. Berghausen, O.: *Streptococcal Septicemia*, *Cincinnati J. Med.* **4**:376, 1923.

17. Eggston, A. A.: *Clinical Pathology of Mastoiditis, with Special Reference to Bacteremia and Treatment by Blood Transfusions*, *Laryngoscope* **40**:424, 1930.

18. Ballenger, H. C.: *Bacteremia Associated with Acute Hemolytic Streptococcal Throat Infections*, *Arch. Otol.* **4**:97 (Aug.) 1926.

and Hirshfeld¹⁹ recently published a study on 150 consecutive cases of sepsis observed in the Mount Sinai Hospital. Their study concerns cases of sepsis produced by various micro-organisms, including 64 cases of *Str. haemolyticus* sepsis, and deals with observations on clinical manifestations of sepsis, treatment, diagnosis and prognosis. Special consideration is given by them to what they termed preseptic and early septic phases of infections when blood cultures may be negative.

METHODS

The bacteriologic picture in the cases which formed the basis of this report was studied in our laboratories by uniform and standard methods. The following technic was employed for blood cultures:

Twenty-one cubic centimeters of the patient's blood was drawn at the bedside from an anterior cubital vein. Fifteen cubic centimeters was divided equally among three 100 cc. Erlenmeyer flasks, the first containing veal infusion broth, p_H 7.2; the second, 2 per cent dextrose-veal infusion broth, p_H 7.2, and the third, 10 per cent tomato extract-veal infusion broth, p_H 7.2. The remaining 6 cc. of blood was equally divided to form three pour plates, 2 cc. being mixed with a tube of 12 cc. of liver hormone-veal infusion agar, p_H 7.4, with a tube of 12 cc. of 2 per cent dextrose-veal infusion agar, p_H 7.0-7.4, and with a tube of 12 cc. of plain veal infusion agar, p_H 7.2, respectively.

Each of the 100 cc. Erlenmeyer flasks contained 90 cc. of fluid medium. In this manner a high degree of partial anaerobiosis was obtained as a result of the small surface exposed to oxygen as compared to the large volume of the medium.

The liver hormone-veal infusion agar was a modification of Huntoon's heart hormone agar, in which the liver was substituted for heart muscle. The final concentration of agar was 1 per cent.

The tomato broth consisted of 80 cc. of 2 per cent dextrose broth and 10 cc. of sterile tomato extract. The tomato extract was made by boiling ripe tomatoes for one-half hour. The fluid extracted in this manner was centrifugated at high speed until the solid matter settled. This procedure usually required at least one-half hour. The supernatant fluid was then filtered through Berkefeld V candles and adjusted to p_H 8.2 before it was poured into flasks. The tomato extract contained a natural useful indicator. The light straw color of the acid extract turned brown during the process of adjustment with tenth-normal sodium hydroxide when the p_H reached between 7.6 and 7.8. The adjustment from p_H 7.8 to 8.2 was then made by means of an indicator. The tomato extract offered valuable ingredients for culture mediums because of the vitamin content (Thj  tta and Avery²⁰ and Schwartzman²¹).

Daily transplants were made for three days from each of the flasks onto slants of 1 per cent dextrose broth-ascitic fluid agar and also into tubes containing 1 per cent dextrose-veal infusion broth. In addition, smears stained by the Gram method were examined daily from each flask containing fluid mediums.

19. Neuhof, H.; Aufses, A. H., and Hirshfeld, S.: Pyogenic Sepsis: Survey of One Hundred and Fifty Cases, *Surg., Gynec. & Obst.* **58**:886, 1934.

20. Thj  tta, T., and Avery, O. Y.: Studies on Bacterial Nutrition: Growth Accessory Substance in Cultivation of Hemophilic Bacilli, *J. Exper. Med.* **34**:97, 1921.

21. Schwartzman, G.: *Proc. Soc. Exper. Biol. & Med.* **22**:7, 42 and 44, 1924

On some occasions the smear from the bouillon-flasks showed gram-positive cocci, which failed to grow on transplants. A certain percentage of these cultures yielded growth on anaerobic subcultures. The failure of the remaining blood cultures to yield growth on various mediums was apparently due to autolysis, which is frequently observed in dextrose and tomato extract mediums. In these instances, as well as in cases clinically suggestive of a general infection (sepsis) but in which blood cultures were sterile, anaerobic blood cultures were made.²² Six additional cubic centimeters of blood was obtained for these cultures and distributed equally among Smith-Noguchi's cooked liver broth and Rosenow's brain infusion broth mediums. Two cubic centimeters of sterile melted petrolatum was poured over the surface of these mediums. On the fourth day the tubes were opened, smears were obtained and subcultures were made from each tube into cooked liver. This procedure was repeated after two days and again two weeks later.

Frequently gram-positive cocci grew in anaerobic mediums, while the aerobic mediums remained sterile. This finding does not signify that the gram-positive cocci thus obtained are strict anaerobes. Although the initial cultivation of these cocci occurred more easily in the absence of molecular oxygen, the streptococci once recovered grew well on further transplants in aerobic mediums.

Str. haemolyticus (*Streptococcus beta-Brown*) was identified by the appearance of the growth of transplants on solid mediums, by the hemolytic effect on the red blood cells on blood agar plates, by the retention of the Gram stain and by the chain formation of the cocci in fluid mediums. The criteria for identification suggested by Brown were followed. In addition, all gram-positive cocci obtained from blood cultures were differentiated from pneumococci by bile and serologic tests.

MATERIAL AND ANALYSIS

This paper presents an analysis of 168 cases of *Str. haemolyticus* bacteremia in which positive blood cultures were obtained, observed at the Mount Sinai Hospital from October 1926 to April 1932. Cases in which the condition was clinically suggestive of *Str. haemolyticus* sepsis but in which no bacteria were found in the blood stream were not included.

In order to classify our material, the term portal of entry was used to indicate the actual site from which *Str. haemolyticus* gained entry into the blood stream. This site need not coincide with the original focus of infection. Thus, an infection may spread by contiguity for a considerable distance from its original site and finally invade the blood stream via a "portal" somewhat removed from the primary infection.

The cases presented herewith were grouped whenever possible according to the portal of entry. Thus, the following classification was formulated.

A. *Str. haemolyticus* bacteremia following peripheral infections, erysipelas, infections of the upper respiratory tract, thrombosis of the

22. Recently anaerobic blood cultures have been included in the routine blood cultures.

lateral sinus, acute otitis media with meningitis, pulmonary infections, osseous and articular infections, surgical infections and gynecological infections.

B. *Str. haemolyticus* bacteremia associated with leukemia, agranulocytic angina, neoplasms, diabetes, rheumatic cardiovascular disease, tuberculosis and unknown causes. In this group no direct relationship could be established between the associated disease and the bacteremia.

Peripheral Infections.—In this group we included all the cases of *Str. haemolyticus* bacteremia in which the condition began with an injury of the epidermis, and an infection of the contiguous soft parts developed later. Of the 22 patients, 14 recovered and 8 died—a mortality rate of 36 per cent. Of the 16 patients whose ages ranged between 1 and 40 years, only 3 died. In the older age group, comprising 6 patients from 40 to 60 years of age, 5 died. It would therefore appear from these figures that the death rate was higher in the patients beyond the fourth decade of life. A careful analysis of the seasonal occurrence of the infections showed no relationship between the severity of the infection and the season of the year.

An analysis was also made according to the localization of the primary focus. In 6 cases the infection originated on the head, neck or trunk, while in the remaining 16 it began on the upper or lower extremities. There was no relationship between the localization of the primary focus and the severity of the disease. In 9 cases *Str. haemolyticus* was isolated from the primary focus as well as from the blood stream. In 3 cases a nonhemolytic streptococcus, *Bacillus pyocyaneus*, and *Staphylococcus albus* were obtained, respectively. These organisms were most likely secondary invaders or contaminants. In the remaining cases bacteriologic studies of the primary focus were not made. Lesions with the portal of entry on the extremities led to multiple and contiguous infections (11 of 16). Infections on the head and trunk remained localized.

Metastatic infections were observed in 7 patients (pulmonary lesions, infections of the bones and joints, meningitis, pericarditis, glomerular nephritis, etc.). Five (71.5 per cent) of the patients died. In contrast to this, only 20 per cent of the patients without metastases succumbed. It is apparent, therefore, that the development of a metastatic lesion was an unfavorable occurrence in this type of infection.

The analysis of the blood cultures with regard to the number of organisms present in the blood stream gave the following results:

In the blood cultures of the patients who died, growth was obtained in all the fluid and solid mediums. Of 17 blood cultures of the patients who recovered, 6 showed growth in only one fluid medium. Of the remaining 11 blood cultures, 4 were positive in all fluid mediums and 7

were positive in fluid and solid mediums. Thus, only in the blood cultures of the patients who recovered was the growth of bacteria limited to fluid mediums (10 of 17).

Erysipelas.—There were 7 cases of erysipelas associated with bacteremia. In 2 the condition followed hernioplasty; in 1 it complicated a carcinoma of the tongue; in 1 it was associated with a weeping eczema of the face, and in another it followed mastoidectomy for pneumococcus type III mastoiditis ("secondary" erysipelas).²³ The remaining 2 cases were instances of typical facial erysipelas with no demonstrable preceding lesion ("primary" erysipelas).²³ Both of these occurred in infants. The blood cultures in both cases yielded growth limited to the fluid mediums. In 1 of the cases the blood culture was positive one day before the appearance of the erysipelas lesion.

In this group 2 patients died—1 of the infants with facial erysipelas and the patient with carcinoma of the tongue.

Infections of the Upper Respiratory Tract.—There were 23 patients with such an infection. Eight died, and 15 recovered. This low mortality, of 34 per cent, attracted attention because of the contrast to the much higher death rates in cases of *Str. haemolyticus* infection originating from other foci. All patients had a history of an infection in the upper respiratory tract. In 20, the infection was diagnosed as pharyngitis without pulmonary involvement. The remaining 3 patients included 2 with tonsillitis, 1 with a peritonsillar abscess and 1 with an infection following tonsillectomy. The foregoing conditions were the only primary foci which could be discovered clinically.

Fifteen patients were between the ages of 1 and 5 years, 6 between 5 and 20 and the remaining 2 were 40 and 72 years old, respectively. There was, thus, an unquestionable predilection for persons in the early years of life. Only 3 cases occurred during the summer and 2 in the fall (November). The remaining 18 cases occurred during the winter and early spring (March and April). This group, therefore, showed a definite seasonal incidence.

We were strongly impressed by the fact that osteomyelitis of the long bones developed in 10 of the 23 patients in this group, and that only 1 of these patients died. Eight of those who recovered were under 4 years of age, and the ninth patient was 6 years old. The patient who died was 11. In each instance only one bone was involved, and the osteomyelitis was either the first or the only complicating condition. Osteotomy and drainage were performed on 8 patients and incision and drainage on 2.

Five of the remaining 6 patients who recovered and 3 of the 8 who died had multiple secondary foci.

23. See the discussion on page 95.

The blood cultures of most of the patients who died showed a considerable number of streptococci in the blood stream. Of the blood cultures of 15 patients who recovered 11 were positive in fluid mediums only and 4 in all mediums. Of the 11 just mentioned, 5 showed growth in only one of the fluid mediums. It is interesting that in the blood cultures of the 9 patients who recovered from osteomyelitis, organisms grew in fluid mediums in only 6 instances.

Thus, we are dealing in this group with a type of *Str. haemolyticus* bacteremia originating in the upper respiratory tract and occurring for the most part in children during the winter and spring months. Apparently, these infections of the blood stream have a favorable prognosis and show a definite predilection for long bones.

TABLE 1.—*Blood Cultures in Cases of Thrombosis of the Lateral Sinus*

Preoperative Blood Cultures				Postoperative Blood Cultures			
Fluid Mediums Only				Fluid Mediums Only			
1 Medium*	2 Mediums†	3 Mediums‡	All Mediums	1 Medium*	2 Mediums†	3 Mediums‡	All Mediums
14	4	15	33	2	3	10	17
Total, 66				Total, 32			

* Usually tomato or dextrose broth.

† Usually tomato and dextrose broth.

‡ Tomato, dextrose and plain broth.

Thrombosis of the Lateral Sinus.—Data as to blood cultures in the cases of this condition are presented for a longer period, of seven years. During this time, operations for thrombosis of the lateral sinus were performed on 63 patients. The results of preoperative blood cultures were as follows:

In 2 cases no blood cultures were taken; in 2 the blood cultures were reported sterile; in 1 *B. pyocyaneus* was isolated, and in another, *B. proteus*, and in 57 cases *Str. haemolyticus* was found in the blood stream in variable numbers. Thus, the preoperative blood cultures were positive in 96.7 per cent of the cases. The large amount of blood taken for cultivation, the employment of a variety of solid and fluid mediums and repeated cultures were all important factors in obtaining this high incidence of positive cultures. In view of the practical importance of a positive blood culture in the diagnosis and operative indication of thrombosis of the lateral sinus, these figures are summarized in table 1.

As is seen from table 1, bacterial growth occurred in fluid mediums alone in 50 per cent of the preoperative blood cultures. Of these positive cultures, 21.2 per cent showed organisms in only one of the fluid mediums. Of the postoperative blood cultures, bacterial growth was restricted to fluid mediums in 44 per cent of the cultures and to one fluid medium in 13 per cent of the cultures.

Further analysis of this group concerns only 43 of the 66 cases which occurred during the five and one-half year period originally considered in this presentation. In these instances, 27 of the patients recovered and 16 died—a mortality rate of 37 per cent. Thirty-three of the patients were less than 15 years of age, and none was over 50. Thus, there was a predilection for the early years of life. There was no predominant seasonal incidence. The main metastatic foci in this group of cases occurred in the kidneys, lungs, bones and joints. Intracranial involvement was the most common fatal complication.

Acute Otitis Media with Meningitis.—There were 4 cases of acute otitis media with meningitis in which numerous streptococci were found in the blood stream. They all resulted fatally. As infection of the middle ear alone does not produce bacteremia, the meningitis had to be considered as the source of the invasion of the blood stream.

All cases occurred in the winter and spring. In 3 cases there were no secondary foci, most likely because of the fulminating course.

Pulmonary Infections.—There were 8 cases of pulmonary infection with a mortality of 100 per cent. The primary foci were bronchopneumonia in 4 instances, a more extensive pneumonitis in 2 and abscess of the lung in 2. Three cases occurred during the winter months and 5 in the spring. The high mortality and the occurrence of the pulmonary infections during the winter and spring months were outstanding features of this group. Only 1 case (i. e., abscess of the lung) followed influenza. All the blood cultures showed numerous colonies in all mediums.

Osseous and Articular Infections.—There were 8 patients with osseous or articular infection, 5 of whom died. Five patients were infants, and of these, 4 died, indicating both the high incidence and the high mortality in the early years of life. No surface infections or infections of the upper respiratory tract were observed clinically. The osseous infections (diaphyses and epiphyses of the long bones, bones of the skull, vertebrae and joints) observed in these cases were considered as primary foci. Metastatic foci, such as bronchopneumonia, abscesses of the soft parts distant to the osseous infections and meningitis, were conspicuous.

Surgical (Postoperative) Infections.—There were 20 cases of Str. haemolyticus bacteremia following various surgical procedures, such as major operations on the genito-urinary and gastro-intestinal tracts, ethmoidectomy and certain minor operations. Seventeen of the patients died, resulting in the high mortality rate of 85 per cent. It was noted that the age and season had no effect on this high mortality.

Metastatic and contiguous infections, in the order of their frequency, were peritonitis, bronchopneumonia, endocarditis and erysipelas.

Gynecological Infections.—In a series of 10 cases of bacteremia which developed following a primary infection of the uterus and adnexa (6 cases of abortion, 2 cases of puerperal sepsis, 1 case of tubo-ovarian abscess with peritonitis and 1 case of endometritis with ovarian abscess), there was a mortality of 60 per cent. Operation was performed on 1 patient only (endometritis with ovarian abscess), and in this case the

TABLE 2.—*Str. Haemolyticus Bacteremia Associated with Miscellaneous Diseases or Occurring as Secondary Invaders*

Diseases	No. of Cases	Portal of Entry	No. of Deaths	Secondary Foci	Blood Culture Mediums	Points of Interest
Leukemia	3	Pharynx, 2 cases; submaxillary infection, 1 case	3	None	All mediums	Age, 46-60
Agranulocytic angina	1	1	None	All mediums, numerous organisms	
Neoplasm	6	Site of operation, 4 cases; cancer of tongue with erysipelas of face, 1 case; cancer of stomach 1 case	5	Pericarditis (sarcoma of femur), 1 case	Fluid medium (recovery), 1 case; all mediums, 5 cases	Age in fatal cases, 37-60; age of patient with cancer of breast who recovered, 25; no case in summer and fall
Diabetes	3	Infection of leg	2	None	Fluid medium (recovery), 1 case; all mediums, 2 cases	Infection of leg
Rheumatic endiovascular disease	2	1	None	Fluid medium (recovery), 1 case; all mediums, 1 case	Bacteremia with acute endocarditis in fatal case; bacteremia with no endocarditis in case of recovery
Tuberculosis	1	Pulmonary tuberculosis	0	None	Fluid medium (recovery)	
Unknown	7	5	Meningitis, 3 cases; acute endocarditis, 2 cases; peripheral abscess, 1 case	All mediums, numerous organisms	Meningitis in 3 infants; all cases in winter and spring

blood culture was positive before the operative procedure. The bacteremia in these cases was complicated by infection of the soft parts, bronchopneumonia or endocarditis.

In this small group of cases the number of organisms present in the blood stream was significant for prognosis. Blood cultures of the 4 patients who recovered showed growth only in the fluid mediums, while those of the patients who died showed numerous colonies on solid mediums as well.

Associated Miscellaneous Nonbacterial Diseases.—In 23 cases *Str. haemolyticus* bacteremia occurred in association with one of several miscellaneous diseases (table 2). The number of cases in each subgroup was too small to permit individual analysis. The primary disease in this group was usually not an infectious process. Invasion of the blood stream occurred secondarily, often shortly before death in patients with markedly diminished resistance.

Seventeen of the patients died. The organism usually grew in all the mediums. In the 4 cases in which organisms were cultivated from fluid mediums only, recovery from the infection took place.

TABLE 3.—*Mortality Rates in Entire Group of Cases*

Group	Number of Cases	Mortality Percentage
Secondary erysipelas	5	20
Infections of the upper respiratory tract.....	23	34
Peripheral infections	22	36
Thrombosis of the lateral sinus.....	43	37
Primary erysipelas	2	50
Gynecological infections	10	60
Osseous and articular infections.....	8	62
Associated nonbacterial diseases.....	23	74
Surgical infections	20	85
Acute otitis media with meningitis.....	4	100
Pulmonary infections	8	100
Total.....	168	54

COMMENT

In these cases of *Str. haemolyticus* bacteremia there was a close correlation between the bacteriologic picture and the clinical significance. We have observed that the occurrence of a positive blood culture with the technic employed indicated a general infection (septicemia) clinically. In this series no positive blood cultures were encountered in cases in which such a general infection was absent.

It should be noted that certain features in our blood culture technic were apparently responsible for the high percentage of positive blood cultures obtained. We refer particularly to the large quantity of blood drawn, the variety and enrichment of the mediums employed, the careful adjustment of p_H of the mediums and the daily subcultures, spreads and prolonged observation. The sensitivity of our routine mediums has been checked at various times by simultaneous comparison of our results with those obtained by a number of recommended procedures,

including the method of Cecil, Nicholls and Stainsby,²⁴ various anaerobic methods,²⁵ and Friedberg's²⁶ recently described method using Kendall's mediums, and none of these showed a higher incidence of positive blood cultures.

The efficacy of our blood culture methods has been demonstrated by our experiences with diseases proved to be associated with bacteremia. Thus, in thrombosis of the lateral sinus, a condition in which the blood stream is invaded at some time during the course of the disease, positive blood cultures were obtained in 96.7 per cent of the cases over a seven year period. Also, during a similar period with which this study is concerned, in 95.5 per cent of the cases of subacute bacterial endocarditis in which autopsy was performed, nonhemolytic streptococci (alpha) had been cultivated from the blood stream by a similar technic.²⁷

We have been especially interested, while studying these blood cultures, in the clinical significance of the growth of hemolytic streptococci in fluid mediums alone as distinguished from growth in both fluid and solid mediums. We have been able to establish certain diagnostic and prognostic criteria from these observations.

Growth in both fluid and solid mediums was interpreted to indicate the presence of large numbers of organisms in the blood stream, whereas growth restricted to fluid mediums indicated a paucity of organisms. This becomes clear when one considers that inoculation of a single bacterium into a fluid medium yields a high concentration of bacteria in from twenty-four to forty-eight hours. On the other hand, similar inoculations into a solid medium will yield only a single colony. Furthermore, the initially inoculated bacterium is much less likely to survive on a solid medium than in a fluid medium.

The most striking observation which this study presents was that every positive blood culture of *Str. haemolyticus* was associated with clinical indications of invasion of the blood stream. In other words, in every case the condition was a "frank" bacteremia and clinically significant, while what is known as a "transitory" and clinically insignificant bacteremia with no evident portal of entry was not encountered. This also applied to cases in which growth was limited to fluid mediums, even to one fluid medium. Thus, in the cases of peripheral infection,

24. Cecil, R. L.; Nicholls, E. E., and Stainsby, W. J.: *The Bacteriology of the Blood and Joints in Chronic Infectious Arthritis*, Arch. Int. Med. **43**:571 (May) 1929.

25. Cohen, J.: *The Bacteriology of Abscess of the Lung and Methods for Its Study*, Arch. Surg. **24**:171 (Feb.) 1932.

26. Friedberg, C. K.: *A Comparative Study of Blood Cultures Taken with Kendall and Routine Mediums*, Arch. Int. Med. **52**:120 (July) 1933.

27. Libman, E.: *Characterization of Various Forms of Endocarditis*, J. A. M. A. **80**:813 (March 24) 1923.

infection of the upper respiratory tract and thrombosis of the lateral sinus, conditions in which a positive blood culture was very important for diagnosis, 48 per cent of the blood cultures were positive in fluid mediums only. Furthermore, in 36 per cent of these positive blood cultures growth occurred in one fluid medium. In every one of these cases the blood stream was being fed by a demonstrable septic focus.

Growth of nonhemolytic streptococci (alpha and gamma-Brown) confined to fluid mediums does not have the same clinical implication as indicated previously for hemolytic streptococci. Such a bacteremia might belong to the transient variety and be clinically unimportant.²⁷ In a recent analysis of cases of nonhemolytic streptococcus bacteremia, Lichtman and Gross²⁸ showed that in a consecutive series of 5,233 blood cultures performed in the laboratories of the Mount Sinai Hospital by the same technic and during approximately the same period as those reported here positive cultures were obtained in only 6+ per cent of the cases of rheumatic fever and other arthritides. On the other hand, in control cases of leukemia, anemia, colitis, meningococcus meningitis and renal infections, approximately the same percentage of positive results was obtained, indicating that the positive blood cultures in both groups were probably obtained in cases of transient bacteremia. Apparently these organisms are common inhabitants of the gastro-intestinal and respiratory tracts and occasionally gain temporary entrance into the blood stream despite the absence of a local infection. Such absorption occurs more readily in the presence of a debilitating disease, in which the barrier between the upper respiratory or gastro-intestinal tract and the blood stream becomes more permeable. The same mechanism probably explains the cases of invasion of the blood stream reported by Epstein and Kugel²⁹ and by Burn.³⁰ Experimental confirmation of this point of view has been submitted by Desoubry and Porcher,³¹ who demonstrated that blood cultures of horses which were positive after a heavy fatty meal became sterile several hours later.

28. Lichtman, S. S., and Gross, L.: Streptococci in the Blood in Rheumatic Fever, Rheumatoid Arthritis and Other Diseases, *Arch. Int. Med.* **49**:1078-1094 (June) 1932.

29. Epstein, E. Z., and Kugel, M. A.: Significance of Postmortem Bacteriological Examination, with Special Reference to Streptococci and Enterococci, *J. Infect. Dis.* **44**:327, 1929.

30. Burn, C. G.: Experimental Studies of Postmortem Bacterial Invasion in Animals, *J. Infect. Dis.* **54**:388, 1934; Postmortem Bacteriology, *ibid.* **54**:395, 1934.

31. Desoubry, M. G., and Porcher, M. C.: *Compt. rend. Soc. de biol.* **47**:101, 1895.

Even this small percentage of blood cultures yielding nonhemolytic streptococci in cases in which they are clinically insignificant must be distinguished from cases of frank bacteremia associated with a septic focus. Such a distinction, especially important in cases in which subacute bacterial endocarditis is suspected, can actually be made on bacteriologic grounds alone. Thus, Libman pointed out that if repeated blood cultures are made in a given case, uniformly positive results with growth in all fluid and solid mediums substantiated the presence of subacute bacterial endocarditis, whereas intermittently positive cultures with growth only in fluid mediums indicated an insignificant transitory bacteremia. The accuracy of this assumption has been repeatedly demonstrated by correlation with the clinical course and autopsy observations. Comparing these observations with the results of our study, we must conclude that whereas the nonhemolytic streptococci in fluid

TABLE 4.—*Relationship of Quantitative Number of Organisms to Mortality Rates (Prognosis)*

Group	Total Cases	Total Mortality Percentage	No. of Fatal Cases	Positive Culture in All Mediums in Fatal Cases	No. of Cases of Recovery	Positive Culture in Fluid Mediums in Cases of Recovery
Infections of the upper respiratory tract	23	34	8	5	15	11
Peripheral infections.....	22	36	5	5	17	10
Thrombosis of the lateral sinus.....	43	37	16	9	27	15
Gynecological infections.....	10	60	6	6	4	4
Associated nonbacterial infections.....	23	74	17	17	6	4
Pulmonary infections.....	8	100	8	8		

mediums only may indicate an insignificant transient invasion of the blood stream, the growth of hemolytic streptococci in fluid mediums indicates a significant frank bacteremia.

It is interesting from a prognostic consideration that the mortality rate was the lowest in the groups of cases in which there was the larger percentage of positive blood cultures in fluid mediums only (peripheral infections, infections of the upper respiratory tract and thrombosis of the lateral sinus). Even in the groups in which the death rate was high, the cases of recovery were usually those in which cultures of the blood showed growth restricted to fluid mediums (gynecological infections, associated nonbacterial diseases). The high mortality associated with the cases of acute otitis media with meningitis and pulmonary infections (100 per cent in our series) is well known. Of special interest because of its clinical importance and comparatively frequent occurrence is the group of surgical postoperative infections, for which the mortality rate, 85 per cent, is the third highest.

Erysipelas.—The question whether the blood stream is invaded by streptococci from lesions of erysipelas is still an unsettled issue. For this reason we are discussing this subject in greater detail.

The early work of Nepveu (1870), Winkel (1886) and Fraenkel (1903) demonstrated the postmortem presence of streptococci in the heart blood of persons who died of erysipelas. Of more interest are studies on antemortem blood cultures. According to Libman,³² positive blood cultures occur in a small group of cases of erysipelas (11 of 100) either as a result of incision into or near carcinomatous tissue or when erysipelas is associated with a chronic disease, such as nephritis or valvular disease, or when mucous membranes are involved. Erb⁸ claimed that bacteremia associated with erysipelas is more likely to occur in infants. Cultures were made in 37 cases by Sprunt (1916),³³ who obtained 5 positive growths. Four of these patients died. Laache (1923)³³ recovered *Str. erysipelatis* from the blood in cases of severe or fatal involvement. Birkhaug (1930)³³ isolated *Str. haemolyticus* (beta) from the heart blood in 8 of 11 fatal cases.

Before discussing the cases of our series it is necessary to establish a possible differentiation between "primary" and "secondary" erysipelas. By primary erysipelas is meant an infection at the site of an unrecognizable or mild local injury, with subsequent invasion of the cutaneous layers and spread by the lymphatic vessels. It is generally accepted at present that this condition is due to a specific etiologic factor. The specificity of the offending organism can be established by serologic studies and by the effect of a specific bacteriophage (Shwartzman,³⁴ Walker³⁵ and Birkhaug³⁶). Duran-Reynals recently demonstrated that filtrates of *Str. haemolyticus* of erysipelas origin and certain other organisms contain substances which enhance cell permeability to a marked degree. These factors may be responsible for the aggressiveness and spreading powers of this streptococcus in tissues of normal resistance. For these reasons it appears that the characteristic pathologic picture in cases of primary erysipelas is due entirely to the spreading

32. Libman, E.: General Infection by Bacteremia, Lectures on Medicine and Surgery, New York Academy of Medicine, New York, Paul B. Hoeber, Inc., 1927, p. 69.

33. Thomson, D., and Thomson, R.: Quoted in *Rôle of Streptococci in Erysipelas*, Ann. Pickett-Thomson Research Lab. 7:1, 1931.

34. Shwartzman, G.: Studies on Streptococcus Bacteriophage: Powerful Lytic Principle Against Hemolytic Streptococci of Erysipelas Origin, J. Exper. Med. 46:497, 1927.

35. Walker, J. E.: Resistance of Scarlet Fever Streptococci to Action of Bacteriophage, J. Infect. Dis. 45:304 (Oct.) 1929.

36. Birkhaug, K. E.: Erysipelas, in Nelson Loose-Leaf Living Medicine, New York, Thomas Nelson & Sons, 1929, vol. 1, chap. 16, p. 447.

property of the invading organism. It appears to us that on the basis of bacteriologic investigations thus far made on the etiology of erysipelas, there is no doubt about the specificity of *Str. haemolyticus-erysipelatis* for primary erysipelas.

The primary type of erysipelas should be sharply differentiated from secondary erysipelas complicating a surgical wound or a lesion of the skin or mucous membrane. In this condition the spreading lesion is apparently due not to the peculiar aggressiveness of the invading micro-organism but to a lowering of the resistance of the tissues by preceding extensive trauma or pyogenic infection. In some of our cases traumatized tissues were infected either by *Str. haemolyticus* or by some other micro-organism (*Pneumococcus*, *Staphylococcus*) long before the lesion of erysipelas appeared. These hemolytic streptococci represented a heterogeneous group of *Str. pyogenes* and could not be identified as the real *Str. haemolyticus-erysipelatis* by bacteriophage and serologic tests.

In the analysis of the positive blood cultures in cases of erysipelas the differentiation just discussed should be kept in mind. During the five years with which this paper is concerned, there were 18 cases of facial erysipelas which could be classified as primary. Blood cultures were sterile in 16 of these and in 2 growth of *Str. haemolyticus* was obtained. The relation of the age to the occurrence of positive blood cultures is noteworthy and corroborative of the observations recorded by Erb. In the 11 cases which occurred in adults, all the blood cultures were sterile. Of the 7 cases in infants, positive blood cultures were obtained in 2. In 1 case the blood culture was positive one day before the appearance of the erysipelas lesion.

It is significant that the number of bacteria present in the blood stream in the 2 cases of facial erysipelas was apparently small as only fluid mediums yielded growth. It seems that in order to obtain positive blood cultures in these cases large amounts of blood should be repeatedly cultured early in the disease.

As evidenced by our series of cases, secondary erysipelas is not infrequently associated with *Str. haemolyticus* bacteremia. This must be borne in mind in the consideration of the differential diagnosis of conditions which include a secondary erysipelas infection.

SUMMARY

In this study 168 cases of *Str. haemolyticus* bacteremia were described and classified according to the portal of entry of the organism.

Ninety-one of the 168 patients died—a mortality rate of 54 per cent. A mortality rate ranging from 60 to 100 per cent was encountered in

the cases of the following conditions: gynecological infections, articular and osseous infections, miscellaneous nonbacterial conditions associated with *Str. haemolyticus* bacteremia, surgical postoperative infections, pulmonary infections and acute otitis media with meningitis. In contrast to these, the mortality rate in the cases of secondary erysipelas was 20 per cent; of infections of the upper respiratory tract, 34 per cent; of peripheral infections, 36 per cent; of thrombosis of the lateral sinus, 37 per cent, and of primary erysipelas, 50 per cent.

Ninety-one per cent of the cases in which the primary focus was located in the respiratory tract (pulmonary infections, infections of the upper respiratory tract, acute otitis media with meningitis) occurred in the winter and spring. The remaining conditions manifested no particular seasonal influence.

Infections of the upper respiratory tract, thrombosis of the lateral sinus and osseous and articular infections showed a tendency to occur during the early years of life. The other conditions evidenced no predilection for a special age. In the group of peripheral infections, the mortality during the middle years of life was considerably higher than during the earlier years of life (75 per cent as compared to 25 per cent).

The enrichments of the blood culture mediums and the blood culture methods employed were largely responsible for the high incidence of these blood cultures which were positive for *Str. haemolyticus*, especially when limited to fluid mediums.

The quantitative estimation of the number of hemolytic streptococci in the blood stream (i. e., growth of the bacteria in both solid and fluid mediums or in fluid mediums only) had both diagnostic and prognostic significance.

The conspicuous groups illustrating the diagnostic value of these blood cultures were the cases of thrombosis of the lateral sinus, infection of the upper respiratory tract and peripheral infection. In the cases of thrombosis of the lateral sinus, 50 per cent of the preoperative blood cultures showed growth in fluid mediums only, and growth appeared in but one fluid medium in 21 per cent of these cultures. In the cases of infection of the upper respiratory tract and of peripheral infection bacterial growth was restricted to fluid mediums in 61 per cent and 45 per cent, respectively, of all cultures.

The prognostic import of the results of these blood cultures is demonstrated by the fact that in the groups in which the mortality was relatively low a high percentage of the blood cultures were positive in fluid mediums only, while in the groups with relatively a high mortality there was a high percentage of positive blood cultures in both solid

and fluid mediums. It is significant that all patients with the gynecological and associated nonbacterial infections whose blood showed growth in fluid mediums only recovered.

Of interest among the cases of infection of the upper respiratory tract was the group in which metastases to the long bones developed. This condition manifested a predilection for young children (10 cases), with a tendency toward complete recovery (90 per cent) and a small number of organisms in the blood stream in a majority of the cases (fluid mediums only 60 per cent).

The data embodied in this paper disclose that in contrast to non-hemolytic streptococci (alpha and gamma) the finding of *Str. haemolyticus* (beta) in the blood stream, even in extremely small numbers, was of important clinical significance for diagnosis, prognosis and indication for surgical intervention.

LATE EFFECTS OF VARIOUS TYPES OF TRAUMA TO THE KIDNEY

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The occurrence of injury to the kidney from physical force presents a problem which may tax the diagnostic experience and acumen of the surgeon to the utmost. The steady rise in the number of automobile accidents throughout the country has led to a corresponding increase in the number of injuries to the kidney, which is reflected in the literature by several reports of extensive series of such cases by Schenck,¹ Osgood and Campbell² and Wood.³ In these reports the physical mechanism of the injury, the difficulties in diagnosis and the possibility of concomitant injury to other structures have been reported in detail. The methods of combating shock, which is present in a high percentage of cases of acute injury, and the points on which the surgeon's choice of operative or expectant treatment is based, are discussed in detail. In most of the series of case reports the discussion of the indications for treatment are based entirely on the extent of the injury received, and little emphasis is placed on the late result of such an injury in the kidney itself or in its surrounding structures. This is natural, as the largest series of cases are reported from the active accident services of busy metropolitan hospitals, in which a follow-up of the late results is practically impossible. Several series of cases of gunshot wounds of the kidney were reported during the World War, but here again emphasis has been laid on the treatment of the acute injury, and no information is available as to the remote effect of the injury on the kidney. The exigencies of the medical service during those days and the fact that such patients who recovered from their injuries were of necessity passed through numerous hospitals would make a follow-up study of the late effects of the injuries extremely difficult to carry out.

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1. Schenck, G. F.: *Traumatic Rupture of the Kidney*, California & West. Med. 40:341-346 (May) 1934.

2. Osgood, A. T., and Campbell, M. F., in Lewis, D.: *Practice of Surgery*, Hagerstown, Md., W. F. Prior Company, Inc., 1929, vol. 8, chap. 5.

3. Wood, Austin: Personal communication to the authors.

During the past few years we have had an opportunity to observe a series of cases in which definite pathologic changes could be demonstrated clinically, in all of which there was a history of more or less severe injury to the kidney at a previous time, and the late results of the injuries in many of our cases have been of such a serious nature that it has seemed advisable to emphasize this aspect of the problem. After a consideration of the series of cases which has been studied, it would seem that at least some of the serious after-effects which have been observed might have been prevented by better surgical methods, instituted either shortly after the injury had been received or at a later period, when the patient's general condition would permit of more active methods.

The tendency toward conservatism in the treatment of injuries of the kidney can be readily understood, and there is no doubt that in many of the cases of less severe injury expectant treatment may be the best choice and may not be followed by any appreciable damage to the kidney and its surrounding structure which can be demonstrated at a later date. The surgeon who attends the patient is preoccupied at first by combating the shock, which is usually present, and if he is successful in tiding the patient over this critical period and avoiding operative intervention it is only natural, as the patient's condition improves and signs of active bleeding have ceased, that he should consider that he has successfully brought the patient through the crisis and that by his judgment an operation has been avoided. Also, from the patient's standpoint it is difficult to understand why, some time after he has been carried through the stage of acute injury, when he may feel himself well on the road to convalescence and complete recovery, operative intervention is advised.

To understand the production of persistent changes in the kidney itself or in its surrounding structures, it is necessary to visualize the possible immediate effects of traumatism to the kidney. Küster⁴ has studied the mechanics of the problem and by his experiments has demonstrated that the kidney filled with blood may be compared to a body of fluid under hydraulic tension, so that on the reception of an injury the "force exerted upon any part of the fluid is transmitted equally in all directions throughout the mass." The possibility of a crushing injury directed through the kidney against the bodies or transverse processes of the vertebrae and ribs is, of course, self-evident.

For practical consideration, three types of injuries to the kidney may be inflicted which will lead to persistent after-effects.

4. Küster: Zur Entstehung der subcutan Nierenzerreissungen und der Wanderniere, Arch. f. klin. Chir. 50:676-686, 1895.

(a) Injuries to the cortex, with rupture of the true capsule, in which more or less extensive extravasation of blood and urine may occur in the perirenal tissues. While undoubtedly small extravasations may be readily and completely absorbed, in cases of more extensive involvement the hematoma thus formed is of such an extent that it will not resolve and will become encysted in time. The precipitation of the calcium in the blood clots, often combined to some extent at least with the urinary salts, may lead to thickening and calcification in the wall of the cyst. The size of the cyst and its adherence to contiguous structures may lead to grave disability. The destruction of renal parenchyma may lead to permanent loss of function. The presence of a calcified cyst closely adherent to the capsule of the kidney may lead to further reduction of function through pressure atrophy.

(b) The parenchyma of the kidney may be torn into the calices or pelvis. In healing, the calices or pelvis may be greatly distorted by scar tissue, eventually causing hydronephrosis, dilatation and distortion or even obliteration of a calix, and during the period when the pelvis is distended with a blood clot and hence draining poorly, urinary salts may be deposited on a portion of the clot and lead to calculus formation. In this type of injury again considerable distortion by scar tissue may result with subsequent permanent diminution of function.

(c) Injuries to the pelvis, or especially the upper portion of the ureter. If the tear is incomplete, subsequent cicatrization may lead to obstruction and hydronephrosis. If the ureter is completely torn across at the time of the injury, the kidney will eventually be completely destroyed. However, there will probably be an extensive peripelvic extravasation of blood and urine.

Figure 1 (from Osgood and Campbell) will help to visualize the main types of injury to the kidney which may be inflicted, but two additional diagrams should be included: one to show injuries of the vascular pedicle and the other to show injuries of the pelvis and ureter. In *A* (fig. 1) tears have been inflicted in the parenchyma with rupture of the true capsule and little or no extravasation. Such an injury might, in all probability, heal cleanly without demonstrable after-effects, provided that the pelvis or calices had not been too badly torn. In *B* multiple complete ruptures of the kidney have been inflicted, and one would expect perirenal extravasation. If the patient did not die of immediate hemorrhage and if operation were not undertaken, the kidney would be completely destroyed and would finally be represented by an atrophic mass of scar tissue enclosed in a cyst, the wall of which would later become calcified. In *C* the cortex and capsule have been ruptured, but the injury has not extended into the pelvis or calices. In case of such an injury bleeding would probably stop when compression

from the perirenal hematoma reached an appreciable degree. The injury of the renal cortex would probably heal with a minimal formation of scar tissue. If the perirenal hematoma were very extensive, it would probably result ultimately in the formation of a calcified cyst adherent to the kidney and distortion of this structure by pressure. In *D* the capsule and parenchyma of the kidney have been ruptured into the pelvis. Here again a perirenal hematoma would be formed, which might result in a persistent calcified cyst. The pelvis has been torn and during the cicatrization might lead to extensive distortion by scar tissue with resulting hydronephrosis. In addition, urinary salts might deposit on the blood clot present and lead to renal calculus. In *E* the parenchyma

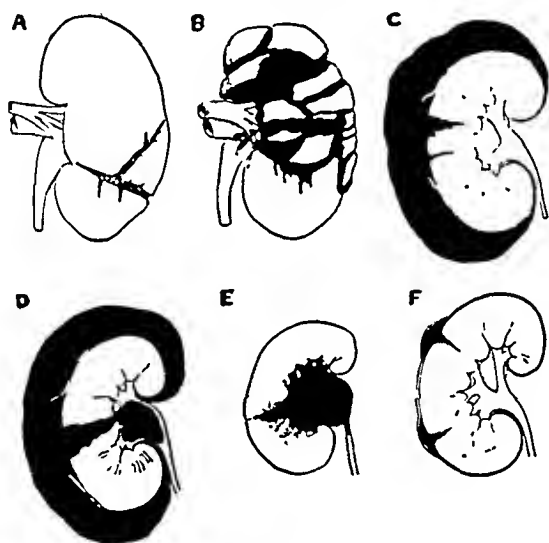


Fig. 1.—The common types of traumatic injury of the kidneys. Reproduced from Osgood and Campbell, in Lewis, D.: *Practice of Surgery*, Hagerstown, Md., W. F. Prior Company, Inc., 1929, vol. 8, chap. 5.

has been torn into the pelvis. The true capsule has not been ruptured, and there will be no perirenal hematoma. In case of this type of injury also the pelvis might be distorted by the subsequent formation of scar tissue, and there is a possibility of the formation of a stone. In *F* two ruptures have been inflicted in the cortex, but the true capsule has not been torn. The after-effect of such an injury would probably be minimal, and extravasation under the unruptured capsule would in all probability produce so much pressure that the bleeding from the tear in the cortex would soon stop. Such an extravasation would probably be easily reabsorbed. There is a possibility that a small cyst might persist.

Tearing injuries of the vascular pedicle usually result in death from hemorrhage. If the patient should survive such an injury, the kidney would of course be necrotic and surrounded by a large perirenal hematoma. Ruptures of a previously normal pelvis would be extremely rare, and it is difficult to understand how such an injury could be received without extensive damage to the kidney. However, in cases of primary hydronephrosis, rupture of the distended pelvis has been frequently reported. Such an injury would lead to extravasation of urine, mostly about the kidney, and the resulting scar tissue would probably further distort the hydronephrosis and hasten eventual complete destruction of the kidney. The ureteral wall may be crushed to such an extent that subsequent cicatrization will lead to traumatic stricture and hydronephrosis. In such cases there would be little or no perirenal hematoma unless the renal cortex had been injured and its capsule torn. Should the ureter be completely severed, there will result a perirenal extravasation of urine, and of course subsequent cicatrization will result in complete destruction of the kidney.

Infection may complicate the picture at any time in any one of these injuries. Should a perirenal hematoma become infected, it will take on the characteristics of a perirenal abscess. The clotted blood is an excellent medium for the growth of micro-organisms, and the injury of the tissue through trauma or from the extravasation of urine would further enhance the virulence of the infection. If infection should supervene either through the blood stream or through a ureteral catheter in a pelvis which has been torn and is filled with a blood clot, pyonephrosis with complete destruction of the kidney may easily develop or the infection may simply tend further to distort and complicate formation of scar tissue.

Distortion of the pelvis or calices will favor the persistence of infection. On account of the interference with drainage and the production of dilated cavities, the changes in the wall of the pelvis or calices due to scar tissue resulting from the injury may also interfere with the natural resistant properties of the tissues.

Eisendrath⁵ recently reported a case of stricture at the ureteropelvic junction with resulting hydronephrosis, which he attributed to an accident twenty years previously, which was followed by severe pain and hematuria of two weeks' duration. The patient was treated conservatively, and the symptoms disappeared. Eisendrath saw the patient after the kidney was transformed into a hydronephrotic sac, as a result either of direct injury to the ureter or of contracture of periureteral scar tissue.

5. Eisendrath, D. N.: Ureteral Stricture and Hydronephrosis as Late Sequel to Kidney Injury, *J. A. M. A.* **104**:1898-1899 (May 25) 1935.

The importance of recognition of a perirenal hematoma after injury to the kidney is suspected has been emphasized by Warner.⁶ Hagner advised expectant treatment in cases of injury to the kidney if the hemorrhage is diminishing in amount and there is no evident perirenal extravasation.

Kemm⁷ reported a most unusual case which illustrates the necessity of continuous observation in cases in which injury to the kidney is suspected, even though clinical improvement may proceed uneventfully. His patient suffered a severe crushing injury to the left lumbar region. Shock lasted for twenty-four hours, and the patient was discharged from the hospital on the sixth day. He was readmitted ten days later in good condition, but with marked swelling of the abdomen, which on examination was found to be due to a tightly encapsulated collection of fluid extending from the diaphragm to the pelvis on the left side. At operation about 2 liters of straw-colored fluid was found surrounding the kidney, which had been completely divided at the junction of the upper and the middle third. The history in this case is similar to that in cases 5, 6, 8 and 10 of our series, in which abdominal swelling was noted some time subsequent to the accident. Had operation not been performed, undoubtedly a large calcified cyst would have resulted.

The effect of infection on the subsequent course in such cases has been emphasized by many writers. Infection of a perirenal hematoma is a serious complication and may lead to extension of the abscess thus formed in many directions along the lines of least resistance. Infection directly introduced into the kidney, as in the case reported by Jeck,⁸ is extremely dangerous, as the devitalized tissue resulting from the injury forms an excellent medium for the growth of organisms. Culver⁹ advised against early ureteral catheterization in dealing with injury to the kidney on account of the danger of introducing infection, but when pain persists after spontaneous recovery he advised that pyelography be carried out to determine whether distortion of the pelvis and calices is present. Woodruff¹⁰ expressed the belief that the subsequent loss of functional ability depends on the type of obstruction of

6. Warner, F.: *Traumatic Injuries of the Kidney*, Boston M. & S. J. **176**: 740 (May 24) 1917.

7. Kemm, N.: *Rupture of the Kidney: Delayed Symptoms; Operation; Recovery*, Brit. M. J. **2**:1218 (Dec. 22) 1923.

8. Jeck, J. S.: *Stab Wound of Kidney: Unusual Complication*, J. Urol. **17**: 449-452 (April) 1927.

9. Culver, H.: *Trauma as a Factor in the Production of Certain Urological Conditions*, Journal-Lancet **50**:379-382 (Aug. 15) 1930.

10. Woodruff, Stanley R.: *The Traumatized Kidney: A Study of the After-Effects*, J. M. Soc. New Jersey **27**:208-211 (March) 1930.

the organ and particularly on infection. He stated that a study of those patients not subjected to nephrectomy who have recovered without the intervention of infection would surely prove that in ordinary cases of rupture of a kidney by far the major number of patients recover without any appreciable diminution in functional ability. If infection involves the parenchyma, pyelonephritis, pyonephrosis and renal calculus may develop. Backus¹¹ reported a case of severe injury to the right lumbar region, followed by shock and hematuria. The patient recovered under expectant treatment, and pyelograms taken one month and two months after the injury showed the gradual development of hydro-nephrosis with contracture at the ureteropelvic junction, which he interpreted as a posttraumatic fibrosis. West¹² stated that after three or four days of conservative treatment in cases in which hematuria persists with tumefaction in the left lumbar region, exploratory operation should be done without further delay, in an effort to control the hemorrhage and prevent infection.

Beretervide¹³ expressed the belief that thickening of the capsule of the kidney associated with pain and diminution of renal function, the syndrome known as nephrosclerosis, occurs as a result of trauma. He reported the case of a man aged 53 who received a severe injury in the right lumbar region, with hematuria persisting for twenty days and pain in the injured side on walking and effort, which persisted for a year and a half. Ureteral catheterization showed marked diminution in the function of the right kidney. Beretervide emphasized the significance of this condition in the work of an industrial accident commission.

In the literature there are a few reports of the development of renal calculus after injury to the kidney. Boshamer emphasized the importance of posttraumatic calculus and mentioned the fact that this condition is rarely mentioned in textbooks. He expressed the belief that a stone may form by deposition of urinary salts on a clot or about a piece of necrosed tissue. If associated injuries to the spine or long bones are present, the probability of the formation of a stone is enhanced, as has been observed in injuries of this type. Dubner¹⁴

11. Backus, H. S.: Traumatic Rupture of Kidney with Symptomatology of Acute Abdomen, with Case Reports, *New England J. Med.* **211**:563-564 (Sept. 27) 1934.

12. West, L. A.: Traumatic Rupture of the Kidney, *J. Iowa State M. Soc.* **25**:90-92 (Feb.) 1935.

13. Beretervide, J. J.: Renal Insufficiency After Trauma, *Prensa méd. argent.* **15**:1438-445, 1929.

14. Dubner, I.: On the Question of True Traumatic Formation of Renal Calculus, *Deutsche med. Wchnschr.* **57**:851-852 (May 15) 1931.

expressed the belief that in every true traumatic renal calculus a nucleus of blood coagulum should be demonstrable in the concrement. He emphasized the fact that renal calculi occur frequently in cases of traumatic transverse lesions of the spinal cord, but quite correctly he did not regard them as true traumatic renal calculi. He reported the case of a patient aged 18 who received a severe injury to the left flank. No definite history of hematuria could be obtained. Two years later the patient began to have severe pains in the left lumbar region at irregular intervals. Roentgen examinations at this time revealed no calculi, but on microscopic examination blood was seen in the urine. The pains continued at intervals, and a year later roentgenograms revealed a calculus in the region of the right renal pelvis. The calculus was removed through a pyelotomy incision, and the specimen consisted of two flat shells of calcification, inside of which an old blood clot was situated.

Bonar¹⁵ reported two cases of retroperitoneal hemorrhage. He described the case of a woman aged 30 whose left eye had been removed for "tubercular trouble" several years previously. She noticed pain in the right loin followed by a swelling on this side of the abdomen five months after a fall. At the time of the original accident she was not severely injured, and no hematuria had occurred. An exploratory laparotomy was done, and it was discovered that a large retroperitoneal hemorrhage had occurred following the trauma. A tumor was later found at the same site. In reviewing this case, however, it seems more probable that the melanotic sarcoma was secondary to a tumor of the eye and that the retroperitoneal hemorrhage occurred spontaneously from extension of the tumor through the capsule and bore no relation to the trauma which had occurred five months previously.

In the following series of cases, a short summary of each of which is given, definite pathologic changes could be demonstrated either on clinical examination or at operation which were definitely correlated to a previous injury to the kidney.

REPORT OF CASES

CASE 1.—A. H., aged 13 years, was admitted to the hospital on July 25, 1933, a few hours after the right side was injured by a fall from a horse. Hematuria persisted for ten days and severe pain for the first few days. The patient was discharged on August 10, free from symptoms and with the urine clear. An intravenous urogram made four months later (November 6) showed hydronephrosis of the upper calices and marked distortion of the lower calix (fig. 2A).

A rupture through the kidney substance, probably into the pelvis, resulted from the accident, and in the process of the formation of scar

15. Bonar, T. D. G.: Two Cases of Retroperitoneal Hemorrhage, *Lancet* 1: 25:90-92 (Feb.) 1935.

tissue, there was distortion of the pelvis and calices. While the patient is free from symptoms at present, it is probable that the hydronephrosis will progress and the formation of a stone is a distinct possibility.

CASE 2.—L. M., aged 27, was admitted to the hospital on Oct. 4, 1929, complaining of dull pain in the left side and cloudy urine. His left side was injured fifteen years previously by a fall. He had severe pain for three days and hematuria for ten days. A plain roentgenogram (fig. 2 *B*) showed a large stone filling the upper portion of the left kidney and numerous small stones in the lower calix. Ureteral catheterization showed marked diminution of function of the left kidney. A pyelogram (fig. 3 *A*) showed marked hydronephrosis and especially distortion of the upper calix. On account of the presence of stone, the reduction in function and the markedly distorted pelvis, nephrectomy was done on November 8.

The stone almost certainly arose as a result of the injury to the kidney. It seems possible that had the kidney been exposed at the time of the accident, with repair of the injury and especially drainage of the pelvis by nephrostomy, the extensive distortion which later necessitated nephrectomy might have been avoided.

CASE 3.—A. R., aged 55, was admitted to the hospital in October 1929 on account of attacks of pain in the left lumbar region. The patient had received a severe injury to the left lumbar region in a motor boat accident six years previously. Hematuria appeared after the accident and persisted for three weeks. One year later calculus was removed through a nephrotomy incision. A roentgenogram (fig. 3 *B*) showed a small stone in the lower calix, and a pyelogram showed definite constriction at the ureteropelvic junction, with early hydronephrosis.

It seems possible that had the kidney been exposed after the accident and the pelvis washed free from blood clots and adequately drained, the subsequent formation of a stone and operation might have been prevented. The stone which is now present will probably grow steadily and necessitate another operation, possibly nephrectomy. The stricture at the ureteropelvic junction, demonstrated by pyelographic study, was probably caused by the formation of scar tissue resulting either from direct injury or from perirenal hemorrhage.

CASE 4.—D. C. entered the hospital on April 7, 1936, on account of recurrent attacks of severe pain in the left lumbar region. He fell from a tree in September 1934, injuring the left lumbar region. He suffered pain for a few days, and blood was present in the urine for three weeks. A pyelogram (fig. 4 *A*) showed an enormous hydronephrosis, with marked distortion and incomplete filling. On account of the fact that the kidney was functionless, nephrectomy was done. The operative specimen (fig. 4 *B*) showed an enormous hydronephrosis, with almost complete destruction of secreting tissue. Marked kinking and obstruction were demonstrable at the ureteropelvic junction. On both the external and the internal aspects of the pelvis there was a large well healed puckered scar. It seems probable that a symptomless primary hydronephrosis was present at the time of the accident, as a result of which the wall of the distended pelvis was ruptured. It would be difficult to conceive of such an injury to a normal pelvis without extensive destruction of the lower pole or midportion of the kidney.



A

B

Fig. 2.—*A*, an intravenous urogram made four months after the accident in case 1. There are moderate dilatation of the upper and the middle calix of the right kidney and marked distortion and irregularity of the lower calix. *B*, a plain roentgenogram made in case 2, showing a large stone filling a portion of the pelvis and a greatly dilated upper calix. Numerous small stones are present in the middle and lower calix.



A

B

Fig. 3.—*A*, a pyelogram showing a large dilatation and distortion of the upper calix with moderate dilatation and clubbing of the middle and the lower calix in case 2. The pelvis and upper portion of the ureter are moderately dilated. *B*, a roentgenogram showing a small stone apparently in the lower calix of the left kidney in case 3.

If exploration had been made in this case soon after the injury, it might have been possible to repair the tear in the pelvis and correct the obstruction at the ureteropelvic junction by an appropriate plastic procedure and, with the institution of drainage, to save the kidney. It would have depended, however, on the findings at exploration and on the amount of undamaged kidney tissue which was present.

CASE 5.—S. R. T., a patient of Dr. Hugh H. Young, was admitted to the hospital in March 1924, at which time a diagnosis of tuberculosis of the seminal tract was made. A radical excision of the seminal tract was done by Dr. Young. The patient was seen again in April 1926, in excellent condition, with the incision well healed. He complained of a dull pain in the region of the left kidney. On further questioning at this time it was brought out that thirty years previously



Fig. 4 (case 4).—*A*, a retrograde pyelogram showing marked dilatation and incomplete filling of the pelvis of the left kidney. The upper portion of the ureter is also dilated and is pushed toward the midline. *B*, operative specimen. The secreting tissue of the left kidney has been practically completely destroyed by hydronephrosis. The pelvis is markedly dilated, and an old puckered scar is present on its internal and external surfaces. There are marked kinking and definite obstruction at the ureteropelvic junction.

he had been run over by a wagon, the wheels passing over the left side. He did not remember the presence of blood in the urine, but a gradual swelling of the abdomen occurred, becoming so prominent that six months later a large amount of fluid was drawn out by a needle on two occasions. For the past few years he had noted a dull pain in the left side of the abdomen and left lumbar region. A stereoscopic roentgenogram showed a large calcified cyst over the left

kidney, apparently closely adherent to its anterior surface. Cystoscopic examination, ureteral catheterization and pyelograms (fig. 5) showed no evidence of renal disease. The kidney was exposed through an extraperitoneal incision by Dr. Young, and a large calcified cyst was found adherent to a scar on the anterior surface of the kidney. On account of the dense scar tissue which bound the cyst to the peritoneum and intraperitoneal viscera, excision was impossible.

It seems probable that the extensive rupture of the kidney occurred at the time of the accident, with resulting perirenal extravasation. A large portion of the fluid resulting from the perirenal extravasation was subsequently removed by tapping, but the walls of the remaining portions of the hematoma became calcified as a result of the changes which took place in the disintegrated blood clot.

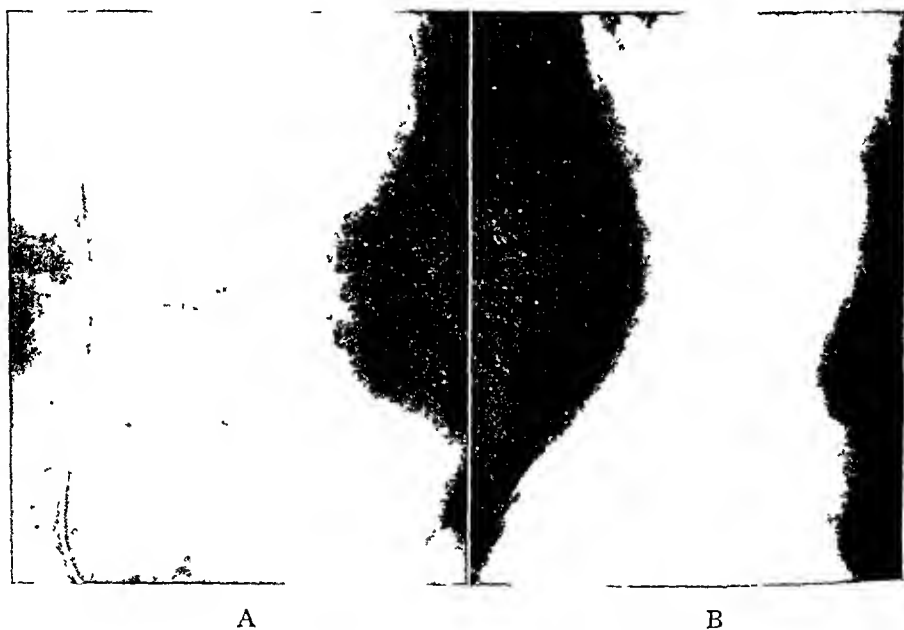


Fig. 5 (case 5).—*A*, a stereoscopic pyelogram of the left kidney. The pelvis is well filled. The calices are cup shaped and normal. No dilatation or other abnormality of the pelvis is seen. The cyst can be seen lying in front of and in close approximation to the kidney. *B*, a lateral pyelogram showing the close approximation of the cyst to the anterior surface of the kidney.

CASE 6.—H. B., a patient of Dr. A. E. Goldstein, was admitted to the Sinai Hospital in February 1926, on account of disability from a large mass in the right side of the abdomen. Twenty-five years previously the patient had been kicked by a horse in the right flank. He was rendered unconscious for some hours and did not remember whether blood was present in the urine. Several days later a mass appeared in the right flank, which slowly increased in size. For the past six months it had caused great discomfort and incapacity. A plain roentgenogram (fig. 6) showed an enormous multilocular calcified cyst occupying the entire right half of the abdominal cavity and extending down below the brim of the

pelvis. On account of the extreme disability and pain, an attempt to remove the cyst was made. The operative procedure resulted in shock, from which the patient failed to rally.

It is evident that had operation been carried out at a time after injury when the patient's condition would permit, the extravasation could have been drained and the blood clot removed and the subsequent formation of this enormous multilocular cyst could have been prevented.

CASE 7.—G. K., aged 38, a patient of Dr. Hugh H. Young, entered the hospital in October 1923 on account of dull pain in the region of the right kidney. Four years previously he had been severely injured about the back and head in an automobile accident. His injuries necessitated hospitalization for several months, during the first few weeks of which blood was present in the urine.



Fig. 6 (case 6).—A plain roentgenogram showing a large multilocular calcified cyst occupying the entire right side of the abdominal cavity.

A stereoscopic roentgenogram (fig. 7) showed a large calcified cyst intimately attached to the anterior surface of the right kidney. On account of the fact that the cyst was causing no severe disability and on account of the technical difficulties encountered in the previous case, no treatment was advised.

If the kidney had been explored after the accident at a time when the patient's general condition was satisfactory, the perirenal clots could have been evacuated with drainage, and the subsequent formation of the cyst would have been prevented.

CASE 8.—S. M. S., aged 21, a patient of Dr. Hugh H. Young, was admitted to the hospital in March 1929 on account of a mass in the left side of the abdomen and numbness of the left leg. Twenty-one years previously he had

been struck in the left side by a sled and was rendered unconscious for a few hours and confined to bed for several weeks, but he did not remember that blood was present in the urine. A large mass gradually developed in the left side of the abdomen, and two and a half years before admission a large amount of fluid was withdrawn by aspiration. A stereoscopic roentgenogram (fig. 8*A*) showed a huge multilocular cyst occupying the entire left side of the abdomen and causing marked scoliosis. Ureteral catheterization showed no function from the left kidney, and on pyelography it was impossible to introduce the medium into the pelvis. It was evident that the left kidney had been completely destroyed. On account of the extreme difficulty and pain caused by the cyst, it was exposed extra-peritoneally by Dr. Young. As much of the walls as possible was excised, the remaining portions of the walls were crushed in and drainage was instituted in such a manner as to marsupialize the remainder of the cavity (fig. 8*B*).

The kidney probably suffered a comminuted injury at the time of the accident, resulting in enormous perirenal extravasation and sub-



Fig. 7 (case 7).—A stereoscopic pyelogram of the right kidney. The pelvis is well filled, the calices are normal, and there is no dilatation or other abnormality of the pelvis. A cyst is seen to lie in close approximation to the anterior surface and convex border of the kidney.

sequent complete destruction of all renal tissue. The consequent formation of a cyst could have been prevented by exposure of the kidney after the accident. It is probable that the kidney would have been found so badly injured that nephrectomy would have been necessary, but this procedure, followed by evacuation of perirenal clots and institution of adequate drainage, would have prevented the subsequent formation of this huge cyst.

CASE 9—J. S., aged 63, a patient of Dr. Hugh H. Young, entered the hospital in October 1930 on account of obstruction to urination. A cautery punch was done with complete relief from symptoms. The patient returned to the hospital in February 1931, complaining of a burning sensation in the hip. On

further questioning it was brought out that two years previously he had fallen from a scaffold and had received a severe injury across the back. He was unconscious for a short time and was incapacitated for four weeks, but at no time was there any blood in the urine. A stereoscopic roentgenogram (fig. 9) showed a small calcified cyst attached to the upper pole of the right kidney. On account of the absence of symptoms, no treatment was advised.

It seems safe to infer from the history that a cortical rupture of the upper pole of the kidney not involving the pelvis was incurred at the time of the accident, and the comparatively small extravasation of blood resulted subsequently in the formation of a small calcified cyst. It is evident that a cortical injury tearing through the capsule, but not

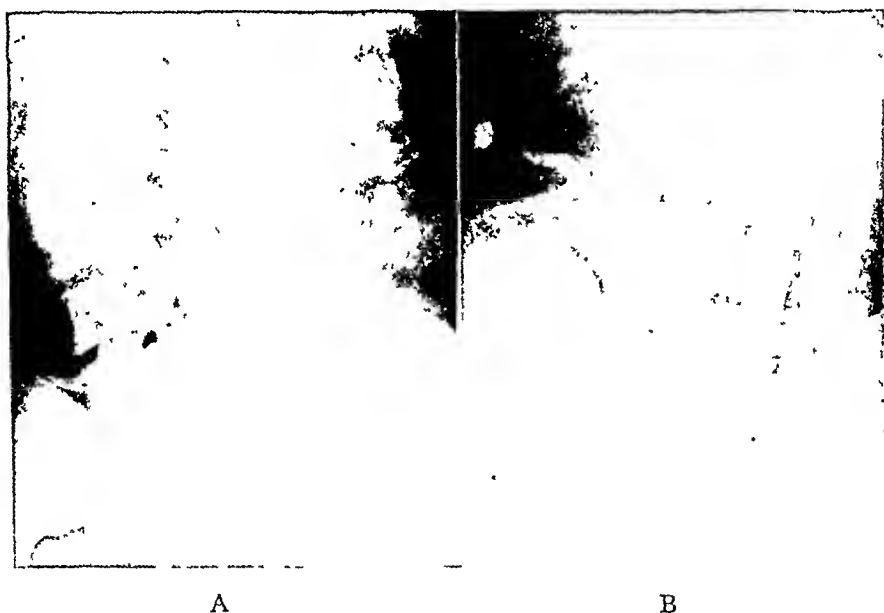


Fig. 8 (case 8).—*A*, a stereoscopic roentgenogram showing a large calcified cyst with irregular margins occupying the entire left side of the abdomen. Only at the upper left border can the cyst margin be definitely made out. The calcification in this case is not so pronounced as in the preceding instances. The size of the cyst caused marked scoliosis. *B*, postero-anterior view taken twenty months after the operation. The outlines of the cyst can no longer be made out. Indefinite calcification is seen in the left side of the abdomen, with marked accentuation of calcification in linear areas as if there had been approximation of the walls of the cyst with intensification of the shadow.

involving the pelvis, might not be accompanied by hematuria, but the resulting extravasation might later lead to the formation of a calcified cyst.

CASE 10.—J. C., aged 21, was seen by Dr. C. A. Waters at the United States Marine Hospital, Baltimore, on account of abdominal pain and symptoms refer-

able to the gastro-intestinal tract. Fifteen years previously the patient was struck by an automobile and severely injured. Exploratory laparotomy was done on the day of the accident, but no injury of abdominal viscera was found, and there was no free blood in the peritoneal cavity. The patient did not remember whether blood was present in the urine. He made an uneventful recovery from the operation, but subsequently a large mass became palpable in the right side of the abdomen. A stereoscopic roentgenogram (fig. 10) showed a large calcified cyst closely adherent to the right kidney.

The patient's general condition at the time of the laparotomy apparently did not permit of careful examination of the region of the kidney. If the presence of a perirenal hematoma had been discovered, evacuation of the blood clots through a lumbar incision and adequate drainage would have prevented the development of this cyst.



Fig. 9 (case 9).—A stereoscopic roentgenogram showing a small calcified cyst with well defined margins lying in proximity to the upper pole and the convex border of the right kidney.

CASE 11.—S., a patient of Dr. Austin Wood, was admitted to the hospital on May 25, 1935, on account of severe pain in the right lumbar region. On April 26 he was thrown from an automobile and received a severe blow in the right side of the epigastrium. He suffered severe pain but was able to walk home. Fresh blood was noted in the urine and persisted for three days, gradually clearing. On May 8 the pain had almost completely disappeared, and the urine was only faintly blood tinged. Physical examination revealed an indefinite sense of resistance over the right kidney, with tenderness, but no definite mass was felt. The urine contained masses of red cells but no organisms. A plain roentgenogram (fig. 11 *A*) showed complete obliteration of the outline of the right kidney and obliteration of the shadow of the psoas muscle. On cystoscopic examination smoky urine could be seen coming from the right ureter. A no. 6 catheter was introduced a short distance up the right ureter, and a pyelogram (fig. 11 *B*) showed marked distortion of the pelvis and obliteration of the calices. An

indefinite shadow extending toward the cortex suggested perirenal extravasation. The pelvis was markedly dilated, and there was probably extravasation around the upper portion of the ureter and the lower pole of the kidney. On account of the definite severe injury to the kidney, immediate operation was advised, but the patient refused to enter the hospital. His condition continued to improve, and the pain disappeared; he resumed his duties as a traffic policeman. On May 25 he was admitted to the hospital in shock, suffering severe pain in the right lumbar region, and the urine was grossly bloody. At operation by Dr. Wood a complete rupture of the kidney was found (fig. 12) at about the junction of the upper and the middle third with extensive comminution. An extensive perirenal clot was found, and active fresh bleeding was encountered, probably coming from the torn vascular pedicle. The clots were evacuated, the pedicle ligated and the kidney removed.



Fig. 10 (case 10).—A stereoscopic roentgenogram showing a large clearly outlined calcified cyst occupying the whole right side of the abdominal cavity. The typical irregular calcification is much more pronounced in the upper portion of the cyst.

It was evident from the plain roentgenogram that an extravasation of considerable degree was present about the right kidney. The pyelogram showed that an extensive comminuted injury of the kidney had been inflicted. Many writers have questioned the advisability of using retrograde pyelography in questionable cases of injury to the kidney on account of the possibility of stirring up bleeding or especially of introducing infection. However, in this case no immediate reaction occurred, and valuable information was obtained as to the extent of the damage done, so that there was no question as to the advisability of prompt operation. Had the patient consented to operation at this



Fig. 11 (case 11).—*A*, a plain roentgenogram showing complete obliteration of the outline of the right kidney and obliteration of the shadow of the psoas muscle. *B*, a pyelogram showing marked distortion of the pelvis with obliteration of the normal shadows of the calices. Apparently there has been extravasation of the pyelographic medium through a transverse rupture at the junction of the upper and middle third of the kidney. There is a large hematoma under the capsule, surrounding the lower pole of the kidney. The pelvis is markedly dilated and distorted, and there is apparently some extravasation of the opaque medium at the region of the ureteropelvic junction.



Fig. 12 (case 11).—Operative specimen showing two complete ruptures through the kidney.

time, his general condition would have been much better than it was when the operation was actually performed. In addition, it seems probable that the operative procedure would have been much simpler because there would have been little or no fresh bleeding with which to contend.

CASE 12.—K., aged 28, a patient of Dr. Austin Wood, was struck with a piece of pipe in the right lumbar region on March 22, 1935. He suffered pain, and the urine showed gross hematuria. A plain roentgenogram (fig. 13 *A*) showed the shadow of the right kidney and the psoas muscle to be completely obliterated. Immediate operation was advised, but this recommendation was disregarded by the general surgeon, and the patient was treated expectantly. He was readmitted to the hospital on May 13. Examination revealed a large mass filling the entire right side of the abdomen, extending to the iliac crest. An intravenous urogram

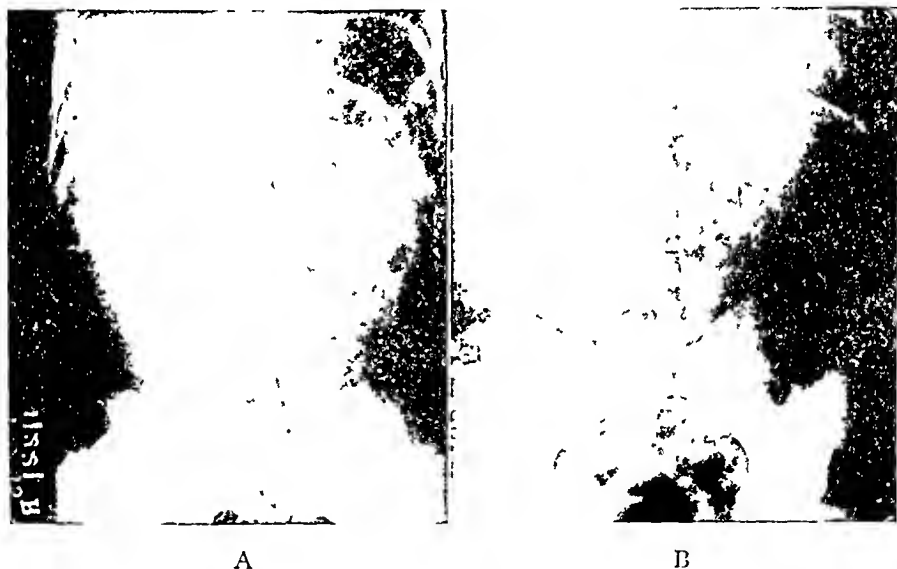


Fig. 13 (case 12).—*A*, a plain roentgenogram made immediately after the accident, showing obliteration of the outline of the right kidney and the right psoas muscle. Gas shadows in the region of the left kidney give a fictitious appearance of a pyelogram. *B*, an intravenous urogram made one month after the accident. No dye has been excreted in the right kidney. The outline of the kidney and that of the psoas muscle are still obliterated. The left kidney shows good excretion, and the calices, pelvis and ureter are normal.

(fig. 13 *B*) showed the obliteration of the shadow of the right kidney and the psoas muscle still present. There was no evidence of excretion of the dye by the right kidney. The pelvis of the left kidney was well outlined and appeared normal. Operation was performed by Dr. Wood on May 20. Approximately 1,500 cc. of extravasated blood and urine was evacuated from around the kidney. The organ was ruptured transversely, and the lower pole was completely separated. Nephrectomy was done. Convalescence was uneventful.

CASE 13.—S. M., aged 37, a patient of Dr. Austin Wood, was injured in an automobile accident in 1933. He was treated expectantly by the family physician for a few days, but was then admitted to the hospital on account of hematuria and pain in the right lumbar region. Roentgen examination and intravenous urograms gave no important information. He was treated expectantly for two weeks and then discharged. He was seen by Dr. Wood on March 25, 1935, two years after the accident. He had had continuous dull pain in the right side since the accident, and hematuria had recurred. A plain roentgenogram (fig. 14) showed the outline of the right kidney to be rather indefinite. The kidney seemed somewhat larger than normal, and opposite the transverse process of the second lumbar vertebrae, apparently in the pelvis, was the shadow of a rather large, soft stone, measuring about 4 by 2 cm.



Fig. 14 (case 13).—A plain roentgenogram of the right kidney. The outline of the organ is rather indefinite, but appears larger than normal. Opposite the transverse process of the second lumbar vertebra is a large stone, apparently in the pelvis of the kidney.

SUMMARY

A series of thirteen cases is presented, in all of which clinical examination or operation has revealed definite pathologic changes either in the kidney or in the perirenal tissue. All of these patients had previously been severely injured in the region of the kidney, at varying intervals of time before the patient was seen. The definite relationship of the trauma to the conditions described in these cases has been established, the conditions encountered varying from those causing minimal disability to those causing complete incapacity. In one patient the condition

which arose as a result of the injury to the kidney was sufficient to cause death, and in most cases operation was necessary.

It is not the purpose of this report to condemn conservative treatment of injury to the kidney. However, the surgeon must be completely familiar with what changes may occur in the kidney or perirenal tissue as a late result of the injuries and should take the proper steps to prevent their development. All cases in which injury to the kidney is suspected should be subsequently studied with special reference to the demonstration of persistent perirenal extravasation. It should be easily recognized by a palpable mass, or the obliteration of the outline of the kidney and shadow of the psoas muscle on roentgenologic examination. In all patients in whom hematuria has occurred as a result of an accident, an injury to the pelvis or calices should be suspected, and subsequent pyelographic studies should be carried out to be certain that distortion or particularly obstruction has not occurred as a result of the formation of scar tissue which may lead to subsequent serious damage to the kidney. In the emergency which exists after any suspected injury to the kidney, in addition to the immediate responsibility, the surgeon should keep in mind a clear perspective of the ultimate changes which may result.

was primarily in the chest or was a herniation of a viscus from the abdominal cavity, pneumoperitoneum was done (fig. 3). This showed no evidence of a hernia, the entire space between the liver and the diaphragm being entirely free.

A study of the literature revealed that in other instances of chylothorax of traumatic origin a cystic mass has been observed in the region of the rupture of the duct and that this mass appeared to communicate directly with the pleural cavity. An example of this is found in the description of the condition found at autopsy in the case of Macnab and Scarlett:⁴

"The lower third of the pleural space was occupied by a well defined cavity which extended to the vertebral column posteriorly and was continuous with the posterior mediastinum. A smaller cavity, about the size of a hen's egg, was located over the body of the tenth dorsal vertebra, in the posterior mediastinum, and was connected with the larger cavity. The walls of the main cavity were about one-eighth of an inch in thickness. The cavity contained partially organized material, which was composed of thin white chylous fluid and masses of coagulated

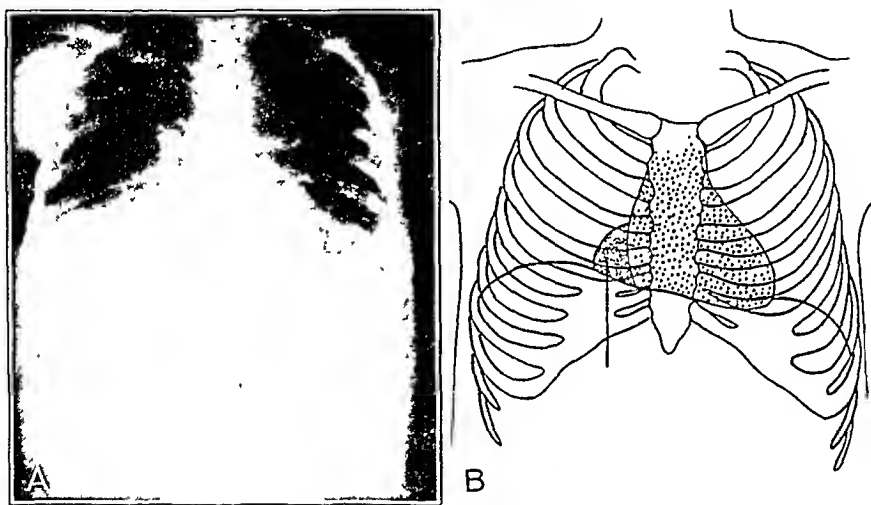


Fig. 2.—*A*, early film showing a rounded mass extending beyond the border of the right side of the heart just above the diaphragm. *B*, a tracing of the x-ray film.

chyle and fibrin resembling large milk curds. Medially, the wall of the cavity was continuous with a mass of low grade inflammatory tissue which occupied the lower third of the posterior mediastinum."

The cases reported previously have a further factor in common with the present case. The accidental force in each instance produced a sudden hyperextension of the spine. It therefore appears possible from anatomic studies that the rupture of the thoracic duct in these instances is brought about by a fixation of that part of the duct which is directly beneath the medial crus of the diaphragm, where in a marked hyperextension of the spine, this firm knifelike edge might so fix on the vertebral body beneath that the duct, being stretched because of the hyperextension, might readily tear or rupture (fig. 4). It was now assumed that this

4. Macnab, D. S., and Scarlett, E. P.: Traumatic Chylothorax Due to Intrathoracic Rupture of the Thoracic Duct, *Canad. M. A. J.* 27:29-36 (July) 1932.

had actually occurred in our patient, as the accident, involving a sudden stop to the machine in which the patient was riding, had produced a sudden flexion followed by hyperextension of her spine.

The patient was obviously suffering from the loss of chyle, but in addition there was a marked decrease in the vital capacity owing to the collapse of the lungs from the chylothorax and the pressure of the chylous ascites. Withdrawal of fluid from either the pleural cavities or the abdomen would give only temporary relief, since the chyle reaccumulated rapidly. It was known from the work of Costain and others, who had suggested external drainage of the thoracic duct in cases of sepsis, that with such free external drainage the incision of the duct usually closed spontaneously after a number of weeks or months.

In view of these facts, it was decided to provide external drainage for this patient as a last hope, the expectation being that if it were possible to drain



Fig. 3.—Pneumoperitoneum demonstrates no evidence of herniation of abdominal viscus into the thorax.

directly at the site of the rupture the symptoms due to the fluid in the chest and the abdomen would be alleviated, and the rupture of the thoracic duct might be given an opportunity to heal.

The following operation was then planned and done to provide the most direct means of access to the site of rupture of the duct without entering either the thoracic or the peritoneal cavity (figs. 5, 6 and 7).

Operation and Course.—The patient was placed in the sitting position with the dorsum of the back arched and presenting at one end of the operating table. Paravertebral nerve block, including the tenth, eleventh and twelfth intercostal nerves on the right, and infiltration of the skin with a 0.5 per cent solution of procaine hydrochloride (total 33 cc. used) were carried out.

A vertical incision was made parallel with and 3 cm. to the right of the spinous processes, extending from the level of the tenth rib to the lower border of the first lumbar vertebra. This was deepened by blunt muscle splitting through the paravertebral muscles. The dissection was then further deepened about 1½ inches (3.8 cm.) below the twelfth rib until the body of the first lumbar vertebra was encountered. Separation was carried on between the crus of the diaphragm and the body of the vertebra. The exploring finger encountered a soft mass of tissue, which was found to lie over the anterolateral aspect of the vertebra. This apparently was the direct site of the rupture of the duct. On further dissection this cystic mass was found to communicate directly with the right thoracic cavity

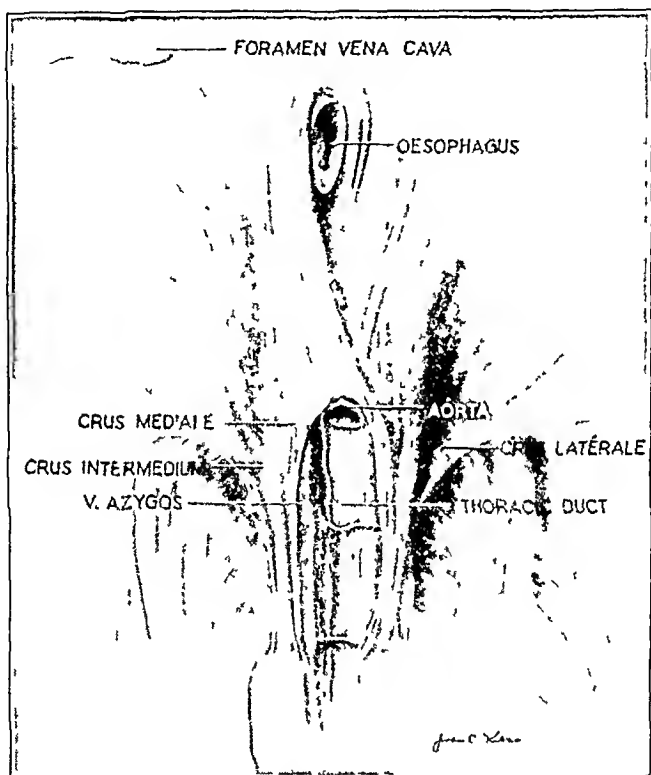


Fig. 4—Anatomic dissection showing the edge of the medial crus of the diaphragm with the thoracic duct passing beneath. It is suggested that in hyperextension of the spine this crus fixes the stretched duct at this point and facilitates its rupture.

The exploring finger could be readily moved up along the bodies of the eleventh and twelfth thoracic vertebrae, and the tissues in the posterior mediastinum had a "pulpy" feel. A large soft fenestrated rubber drain was inserted into the posterior mediastinum up to the opening into the right pleural cavity and was fastened in place with silkworm gut sutures. The wound was approximated in layers tightly around the tube. The patient left the operating table in good condition.

The patient withstood the operative procedure, which had been carried out under paravertebral nerve block alone, remarkably well. Unfortunately, however, the following day, while straining at the stool, she suddenly died, the immediate

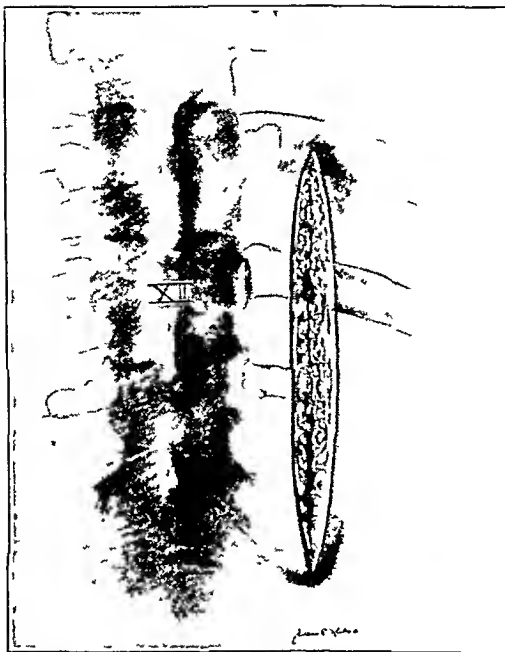


Fig. 5.—Diagrammatic representation of the position of the skin incision with relation to bony landmarks.

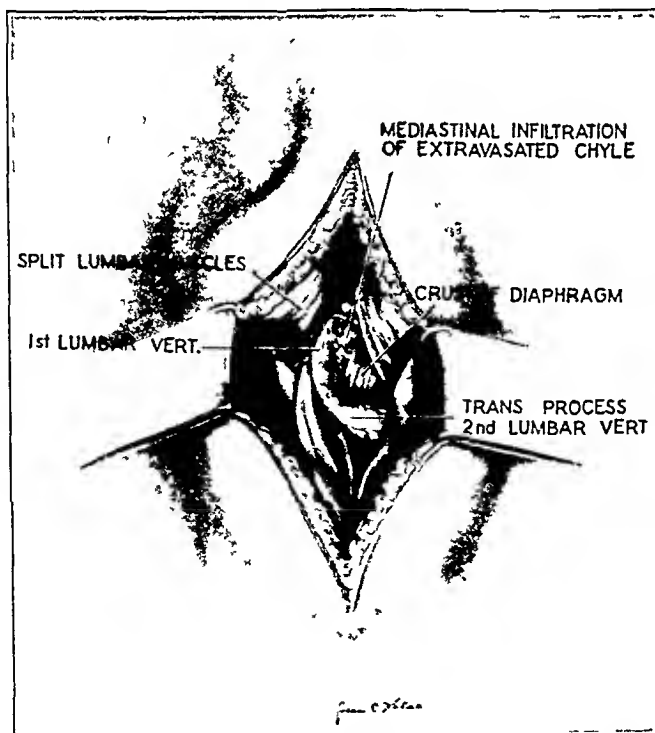


Fig. 6.—Operative approach to the area of extravasated chyle as seen when this mass is first observed.

cause of death being shown at autopsy to have been adrenal apoplexy. Autopsy was done by Dr. J. L. Carr, pathologist to the coroner, the following observations being made:

Postmortem Examination.—There was a recent incision, evidently surgical, 5 inches (12.5 cm.) long in the right costovertebral angle, with a rubber drain in it. There were a scar from an old midline abdominal incision 7 inches (17.8 cm.) long and a scar from an old incision 8 inches (20.3 cm.) long over the anterior surface of the right humerus. There were two recent incisions, evidently surgical, each about 1 inch (2.5 cm.) long, in the right antecubital fossa and one about 2 inches (5 cm.) long on the right femur. When the thoracic duct was dissected out an interruption in continuity was found about 2.5 cm. above the diaphragm. There was some fibrosis about the distal end of the broken area apparently occluding the lumen. The proximal end still showed a tiny patent lumen, although there had been some desmoplastic reaction about it.

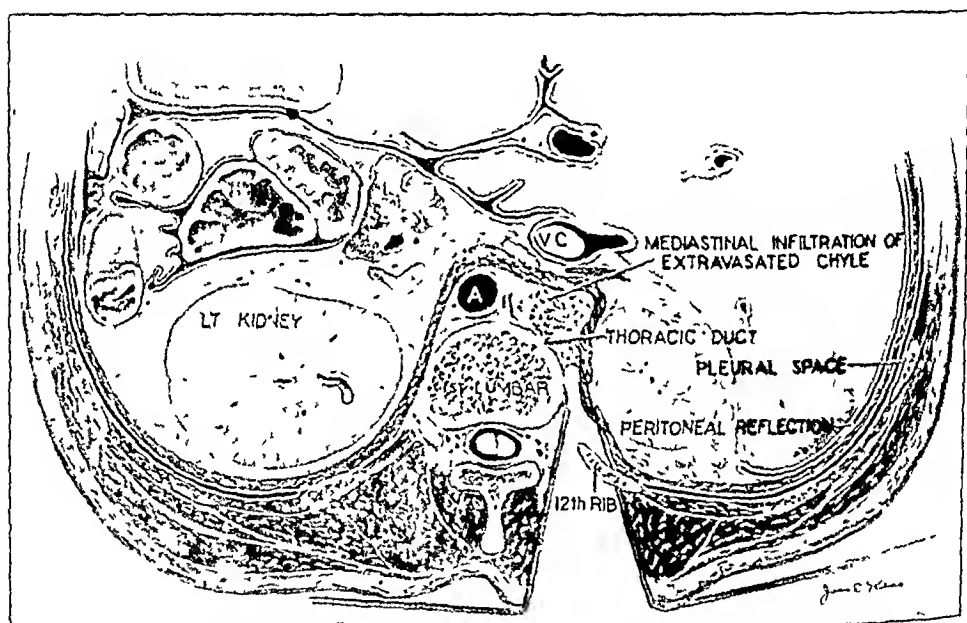


Fig. 7.—Cross-section at the level of the first lumbar vertebra showing (1) location of the extravasated mass of chyle in the mediastinum just above the crus of the diaphragm and (2) the operative incision for drainage of this area without entering either the pleural or the peritoneal cavities.

There was chylous fluid in both the pleural cavities and the peritoneal cavity, that in the pleural cavities being much thinner. All the organs were sent to the pathologist for fixation and examination.

Gross Examination: Specimens were submitted from the heart, lung, liver, spleen, pancreas, kidneys, bowel, uterus and ovaries for study. The heart was very small, weighing 180 Gm. It measured $2\frac{1}{2}$ by $2\frac{1}{2}$ by 4 inches (6.3 by 6.3 by 10 cm.), lay in a clean pericardial sac and had normal vessels and a rather thin and pale but otherwise normal pericardium. The endocardium and valves showed no changes. Both lungs were collapsed and weighed about 225 Gm. apiece. There were massive old adhesions about the base on each side. On the right there was

also a dense succulent mass of adhesions which were at least a month old. A rubber tube ran from this mass out through the right costovertebral angle. The liver was pale and swollen and showed a cloudy swelling of the cells. The capsule was thin, and the edges were blunt. The organ weighed 1,400 Gm. The spleen weighed 60 Gm. and showed a few perisplenic adhesions, moderate thickening of the capsule and rather congested pulp. The pancreas was normal in size, shape and position but was very hard owing to the loss of fat. The adrenal glands weighed about 15 Gm. apiece and showed unusually thick lipoid-filled cortices and fresh hemorrhage occupying the medullary and inner cortical zones. The kidneys showed no significant changes. The uterus, ovaries and tubes were normal except for edema. The intestines showed intense edema, vascular congestion and dilatation of the lacteals.

Histologic Examination: The lungs showed heavy pleural fibrosis. There was partial atelectasis, with many large endothelial cells in the alveolar spaces. The bronchial epithelial cells were desquamated and degenerated. In one area the pleura showed a fibrinopurulent exudate as well as fibrosis. There was a moderate cloudy swelling of the parenchyma of the liver, and a rather heavy deposit of fat was seen in the cells of the periphery of the lobules. There was no cirrhosis or evidence of infection. The spleen showed a pulp heavily infiltrated with lymphocytes and red cells. There was some fibrin on the capsule. The pancreas showed normal cords, ducts and islands. There were no pathologic changes in the kidneys, but the adrenal glands showed a general cellular degeneration with massive hemorrhage throughout both cortical and medullary zones. The capsule showed a little fibrosis, and outside the capsule in the periadrenal fat were thick nests of lymphocytes and deposits of fibrin and red cells. The ovaries and uterus showed no variation from the normal, but corpora lutea were found. Sections of the bowel were normal.

The following diagnosis was made: rupture of the thoracic duct with chylothorax; chyloperitoneum; emaciation; inanition; fatty infiltration of the liver; fibrinopurulent pleuritis, and terminal, fatal bilateral adrenal apoplexy.

COMMENT AND CONCLUSIONS

Rupture of the thoracic duct may occur because of hyperextension of the spine during an accident, the mechanism producing the rupture probably being aided by a fixation of a part of the duct between the tense and the sharp medial crus of the diaphragm anteriorly and the vertebral body posteriorly (fig. 4).

After rupture of the duct there is a localized extravasation of chyle, which persists for some days or weeks before the tissues of the mediastinum and pleura become sufficiently macerated and the fluid finally penetrates into the pleural cavity.

Early in the process the cystic extravasation of chyle may be detected in a roentgenogram (fig. 2A).

Early discovery and drainage of this cystic mass may obviate the later complications of chylothorax and chylous ascites and allow the rupture of the duct to heal spontaneously.

Autopsy in the case reported in this paper showed that chyle may be extravasated either because of a direct rupture of a chyle duct (causing in this case escape of chyle into the thoracic cavities) or by back pressure. (Here the duct was obstructed below the level of the diaphragm, and the abdomen was filled with chyle.) This patient hence exhibited both possible means of extravasation of chyle.

An operative procedure and approach for drainage of the usual site of traumatic rupture of the thoracic duct are presented and illustrated.

An unusual case of combined bilateral chylothorax and chylous ascites is reported.

INTRA-ABDOMINAL ADHESIONS

AN EXPERIMENTAL AND CLINICAL STUDY

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FLINT, MICH.

The formation of adhesions in the abdomen is a necessary reaction between apposing serous membranes, localizing bacterial invasion and limiting the effect of trauma. Where serous membrane is lacking, a far higher mortality prevails if the abdomen is invaded by infection or is subjected to trauma; therefore, surgical approach in the abdomen should and often is initiated by artificial stimulation of localizing adhesions, as in operations on the pharynx and the esophagus. Persistence of adhesions after the protective phase is passed, especially in structures that depend on the anatomic lumen, may become disastrous, as in the cerebrospinal system and in the gastro-intestinal or the genito-urinary structures. Harassing adhesions follow especially infections of the intra-abdominal viscera or trauma. Ever since intra-abdominal operative procedures became the method of choice in dealing with infections and trauma of the peritoneal cavity, the surgeon has observed that a seemingly successful treatment often results in persistent adhesions, which, in themselves, form a barrier to full recovery and necessitate frequent operations for the release of obstructive bands. Reports in the surgical literature are replete with accounts of cases in which operation has been performed for persistent obstructive adhesions. In one of these reported cases, I operated four times for adhesions, and the same patient was operated on four times by other surgeons. There are many patients in whom frank obstructions do not develop but who have partial obstructive lesions and consequently lead a semi-invalid life, often being branded as malingerers or psychopathic subjects. Dr. Charles Mayo once remarked: "Adhesions between movable viscera are of little consequence, but adhesions between abdominal viscera and a fixed point are sources of danger." As stated, peritoneal adhesions are the result of a natural phenomenon, but their persistence results frequently in complete or in incomplete obstruction of the bowel with the resultant chain of pathologic sequelae that are all too familiar.

Read before the sixth congress of the Pan American Medical Association, July 1935; also before the following medical societies in part or as a whole: Livingston County Medical Society, Michigan; Peoria Medical Society, Illinois; Schenectady Medical Society, New York; Marion Medical Society, Ohio.

Conducive to the formation of persistent adhesions are the following: (1) visceral perforations, with a resultant outpouring of intraperitoneal fluid, which becomes infected and literally bathes the contents of the abdomen with pus, causing violent reactions in the serous membrane; (2) drains stimulating the formation of thick local adhesions about them, followed by puckering and fibrosis and inflammatory processes, such as appendicitis, cholecystitis or infiltrating growths, and (3) rough handling of the peritoneal contents or massive removal of the contents, with resultant cooling of great areas of the intestinal tract. Powerful spread with retractors causes injury to wide areas of the peritoneum as well as has a paralyzing effect on the intestinal canal, with ballooning out of the intestines so that close contact minus peristalsis allows agglutination.¹ I am especially partial to spinal anesthesia in operations on the abdomen because intra-abdominal manipulation is facilitated by the great abdominal relaxation, as well as the contraction of the abdominal viscera.² Antiseptic solutions used in the preoperative preparation of the skin, which become dissolved in moist gauze and seep into the abdominal cavity, no doubt contribute to the formation of adhesions. The disastrous results in some patients who were successfully carried through catastrophic perforations of gangrenous appendicitis and later had symptoms of partial or complete obstruction are well known. Hertzler³ demonstrated that fibrinous response in intestinal suture is complete within two hours, and Senn⁴ demonstrated firm adhesion between peritoneal surfaces within from six to twelve hours.

In a recently published study of tissue reactions to drains, Spellman⁵ noted the varied reactions of tissue to different types of drains, rubber drains delaying local repair and the formation of adhesions. Coffey⁶ made use of the so-called Coffey quarantine drain in surrounding wicks of gauze with gutta-percha at the seat of infection, and in many cases he was able to check on the absence of adhesions on reoperation in following years. Of course, in by far the greatest percentage of cases

1. Benjamin, A. E.: Postoperative Peritoneal Adhesions, *Minnesota Med.* **17**:4 (Jan.) 1934.

2. Bogart, Leon M.: Spinal Anesthesia, *Am. J. Surg.* **18**:79 (July) 1932.

3. Hertzler, A. E.: *The Peritoneum*, St. Louis, C. V. Mosby Company, 1919, vol. 1.

4. Senn, quoted by Ochsner and Garside.¹⁰

5. Spellman, A. E.: Selection of Drainage Material, *Arch. Surg.* **28**:837 (May) 1934.

6. Coffey, R. C.: Abdominal Adhesions, *J. A. M. A.* **59**:1952 (Nov. 29) 1913.

the protective adhesions become digested or stretched out and are of no significance, but in from 2 to 5 per cent definite symptoms persist, owing to the fact that the adhesions change from a fibrinous to a fibrous character, and in many cases intestinal obstruction results. There are also a definite number of persons who are operated on who seem to have a predisposition to the formation of a thick scar, thick fibrous bands, or a keloid scar. In one of the cases reported, a woman had had a thyroidectomy performed elsewhere, with the formation of an unsightly, thick, painful keloid scar, which I resected and immediately treated with the roentgen rays. After a laparotomy, the same kind of a scar developed, and the patient suffered from symptoms caused by adhesions, until she was reoperated on and treated as outlined. In the case of an acute intestinal obstruction no hesitancy is experienced by the surgeon in advising a life-saving operation, but in the case of chronic involvement in which the division of adhesions is followed by reformation, surgical intervention is not indicated unless means of prevention of the reformation are possible. The cut adhesions become covered with fibrin, resulting in fibrous tissue, and the cycle begins anew. To reiterate, in many of the cases adhesions are due to injudicious handling, to contamination of the viscera with antiseptic solutions used to paint the skin or to the barbaric use of retractors, the stretching and traumatizing of the tissues being limited to the degree to which the intern pulls on the retractors or to the ability of the instrument to expand.

The endothelial cells forming the peritoneal surface are easily injured by trauma or infection as well as by prolonged exposure to the air, with resultant dehydration and cooling and subsequent healing if followed by the formation of thick fibrous bands. Blood left in the peritoneal cavity is considered by some to be conducive to deposits of fibrin, with the resultant formation of adhesions, though I have consistently left blood in the peritoneal cavity in cases of ectopic gestation and three times in instances of traumatic rupture of the spleen, with apparently no ill after-effect and an excellent immediate effect (clots were always removed). Careful peritonization of raw surfaces is a most essential preventive measure and should be done meticulously if possible. If sufficient peritoneum is not available, omentum attached or grafts should be used to cover raw surfaces.⁷

Various substances were used by the older surgeons to prevent adhesions: olive oil, liquid petrolatum, the so-called Cargile membrane (sterilized ox peritoneum), camphor liniment U. S. P., acacia U. S. P.,

7. Freeman, L.: Use of Free Omental Grafts, *Ann. Surg.* **63**:83, 1916.

etc. Norris and Davison⁸ reported two cases in which liquid petrolatum was used and in which peculiar nodules developed which were similar in appearance and histologic structure; the adhesions reformed in greater degree. Several years ago I used ascitic fluid obtained from a patient with cardiovascular disease in two cases of severe adhesions, with good clinical results.

Substances tried heretofore were used with the idea of forming a protective coat until a certain amount of healing occurred in the raw surfaces. Most of these substances failed, owing to the severe reactions evolved.

The character of the fluid after bacterial invasion differs so that a streptococcic infection is less productive of adhesions than infections with colon bacillus. Not all infections or injuries evoke a similar response, because in cases of peritonitis caused by a streptococcic infection the exudate is poor in fibrin and leukocytes, and the adhesions formed are not formidable, while infection with colon bacilli causes an exudate rich in fibrin and leukocytes, resulting in localization and the formation of fibrous bands. The surface of the peritoneum is almost the same as that of the skin and is capable of secreting a lubricant fluid in which the abdominal organs move. It also has great absorptive power. In a localized infection or irritation there is an outpouring of the peritoneal fluid, absorption also taking place; that which remains forms a protective zone, sealing the omentum and loops of the bowel around the area, forming a barrier, or, as Coffey expressed it, nature's quarantine. The remains of nature's quarantine process, unless absorbed or stretched out, remain as abdominal junk, a descriptive term applied to them by Joseph Price. It is claimed by some authorities that persons with exceptional reparative powers are more prone to the formation of adhesions, the local reaction to injury, mechanical or bacterial, producing a greater response. Adhesions are produced in the dog less readily and rapidly than in the hog, but the latter is far more susceptible to sepsis. In acute and virulent processes, the spread of the inflammation becomes limited only by distant formation of adhesions away from the violent attack, as noted by Curtis⁹ in the thick dense adhesions formed between the liver and the parietal peritoneum, the result of a gonococcic infection of the pelvic organs. Extension from within the lumen may penetrate through the serosa, the lumen of one loop prac-

8. Norris, J. C., and Davison, T. C.: Peritoneal Reaction to Liquid Petrolate, *J. A. M. A.* **103**:1846 (Dec. 15) 1934.

9. Curtis, A. H.: Adhesions of Anterior Surface of Liver, *J. A. M. A.* **99**:2010 (Dec. 10) 1932.

tically forming one inflammatory mass with the lumen of another loop, the infection resulting in a very thick fibrous adhesive band.

The functions of the organs contained in the peritoneal cavity are the preparation and the absorption of food and the elimination of the wastes resulting from the foregoing functions. Disturbance of any one of these functions usually results in disturbance to the others. Freedom on motion of the alimentary tract is most essential, especially of the large bowel, because the posterior half of the lumen of the large bowel is semiattached, acting as a trough. Therefore, adhesions causing attachment to the upper surface of the serous covering render the large bowel almost pipelike, and propulsion is lost by that portion, with dilatation above and below the formed attachment. Ochsner and Garside¹⁰ found that theoretically the use of a digestive ferment is fully justified because of its ability to destroy fibrin. Yardumian and Cooper¹¹ reported the experimental use of pepsin extracted with water and glycerin as successful in 62 per cent of a total of one hundred and eighteen operations on forty-four rabbits.

Wangensteen¹² cited five cases of postoperative adhesions in which 1,000 cc. of air was injected into the abdomen and the patient's buttocks were elevated on two pillows, causing the air to be interspersed between the umbilicus and the bowel; good results were obtained in one case. I believe that this method is faulty because the worst adhesions do not necessarily appear between the bowel and the parietal peritoneum. In my own cases I have often seen adhesions between the small and the large bowel practically covering the anterior portion of the ascending and the descending colon. In several of my cases there have also been severe adhesions between the duodenum and the bed of the liver after cholecystectomy. In one case in particular the adhesions in the upper right quadrant were so thick that it was impossible to divide them without causing injury to the bowel. The patient was treated with a solution of papain over a year and a half ago and has apparently been well since. This observation is opposite to the view held by Fausel,¹³ who, experimenting with papain, found that it acts

10. Ochsner, A., and Garside, E.: *Peritoneal Adhesions*, Surg., Gynec. & Obst. **54**:328 (Feb.) 1932.

11. Yardumian, K., and Cooper, D. H.: *Pepsin in Prevention of Abdominal Adhesions*, Arch. Surg. **29**:264 (Aug.) 1934.

12. Wangenstein, O. H., in discussion on Benjamin.¹

13. Fausel, E. G.: *Experimental Postoperative Adhesions*, M. Times & Long Island M. J. **62**:1 (Jan.) 1934.

decidedly in the prevention of experimental adhesions but has no action on formed adhesions which have not been divided.

Rea and Wangenstein¹⁴ also reported the successful use of a 1 per cent solution of sodium ricinoleate (castor oil soap), papain 1:50,000, a merthiolated solution of amniotic fluid of cow's and defibrinated rabbit's blood. All of these were found to prevent the formation of experimental adhesions. The authors are especially partial to sodium ricinoleate, because they found it just as valuable in the presence of infection as when no infection is present. All the other substances mentioned are not effective in the presence of infection. The clinical applications of sodium ricinoleate have been too few, and Rea and Wangenstein drew no conclusions; the amount used was 60 cc., which was poured into the abdominal cavity before closure.

Ochsner and Garside,¹⁰ Kubota¹⁵ and Walton,¹⁶ after experimentation with enzymes, concluded that papain (a vegetable enzyme) is by far the most suitable for clinical use, being superior to trypsin (animal enzyme) in that its effectiveness is of longer duration. Parke, Davis & Co., in cooperation with Walton and Ochsner, produced a sterile standard preparation which I have been able to use in my experimental and clinical application. The ampules contain 0.25 mg. of papain. The effect of papain, according to Walton,¹⁷ is supposed to be due to a direct proteolytic action, and the concentrations used varied from 1:25,000 to 1:50,000. Concentrations stronger than these will cause, in many instances, irritation and peritoneal bleeding. Papain is derived from the unripe fruit of the papaw tree; it is active in neutral and alkaline mediums.

The early workers with papain encountered a great deal of difficulty in obtaining a solution of the powder supplied in the ampule. After trying many solutions I finally concluded that sodium citrate in a 0.25 per cent solution in distilled cool water forms the best base. This can be obtained by shaking the powdered papain into a wide vessel containing 500 cc. of 0.25 per cent citrated distilled water and agitating slowly and then adding the solution to 1,000 cc. of distilled water,

14. Rea, A. E., and Wangenstein, O. H.: Comparative Efficacy of Substances Employed in Prevention of Intra-Peritoneal Adhesions, *Proc. Soc. Exper. Biol. & Med.* **31**:1060 (June) 1934.

15. Kubota, quoted by Walton.¹⁶

16. Walton, R. P.: The Behavior of Papain in the Peritoneum, *J. Pharmacol. & Exper. Therap.* **43**:487 (Nov.) 1931.

17. Walton, R. P.: Papain Preparations Suitable for Prevention of Adhesions, *Proc. Soc. Exper. Biol. & Med.* **28**:922 (June) 1931.

making 1,500 cc. in all of 1:25,000 solution, which is the strength advocated.

Walton¹⁶ found that the concentration of 1:500 produced a fall in blood pressure, a fall in temperature of from 1 to 1.5 C. and hemorrhagic infiltration as well as edema and partial digestion of the wall of the intestine.

INDICATIONS FOR OPERATIVE PREVENTION OF ADHESIONS

Previous intra-abdominal operations followed by symptoms clearly pointing to obstructive adhesions and interference with the normal physiology of the alimentary tract are indications for the operative prevention of adhesions. The pain may be more or less constant at the site of the previous operation, or it may be distant from it. Acute

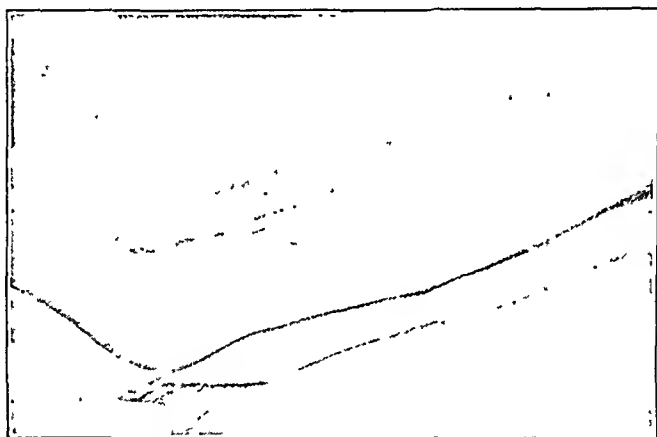


Fig. 1. (patient 10).—Photograph showing a xeloid scar before operation on Sept. 26, 1934.

exacerbation of the pain characterized by cramplike seizures, followed by periods of comparative freedom from pain, are quite characteristic of obstructive lesions of the alimentary tract. Vomiting may be a late symptom and should not be used as a criterion. One or two stools may be effected with enemas, and yet obstruction may be present. Frequent seizures of the aforementioned type are practically pathognomonic of obstruction of the bowel. It is not wise to wait for complete obstruction of the bowel before an operation is decided on, nor should one wait for the symptoms of deep shock to appear before operating. In cases in which gangrene of the bowel is present, the solution of papain and sodium citrate is not indicated and should not be used, as the fluid becomes infected and helps spread peritonitis.



FIG. 2 (patient 10).—Photograph showing the open abdomen on the same date. Note the adhesions.



FIG. 3 (patient 10).—Photograph taken at operation six months later for postoperative hernia. Note the absence of adhesions.

TECHNIC OF PROCEDURE

If possible, the patient should be prepared two or three days prior to operation with a bland nonresidue diet. Saline cathartics are indicated, and two enemas should be given daily. A thorough deflation of the bowel is very helpful. To complete deflation of the alimentary tract, gastric decompression by instituting constant gastric drainage may have to be done. Two doses of pitressin the day before the operation and one dose on the operating table help to keep the bowels contracted and make the operative procedure much easier.

The usual preparation is done, care being taken to remove any excess of the antiseptic used and to dry the skin well. Entrance into the abdomen is best gained by the resection of one of the old scars



Fig. 4 (rabbit 1).—The normal appearance of the abdominal contents of a rabbit.

through its full thickness, so that the scar tissue of the peritoneum is also removed. Sharp dissection of all adhesions and removal of all tags should be practiced; oozing should be stopped with the administration of epinephrine or slight pressure; all clots must be removed. One should refrain from using any retractors intraperitoneally or from manipulating the bowel any more than is needed. The omentum must be dissected free from adhesions so that it is mobile. One should be especially careful to effect thorough dissection of the adhesions around the large intestine during the operation. The bowel must not be brought outside of the abdomen, and any handling of the bowel should be done with wet gauze without excessive pulling or tugging. Good relaxation is imperative, and for this reason in most of my cases operation was done with the patient under spinal anesthesia, as it affords



Fig. 5 (rabbit 2).—Massive formation of adhesions three weeks after irritation plus the introduction of pus followed by the introduction of a solution of papain and sodium citrate used and separation of the adhesions.



Fig. 6 (rabbit 3).—Photograph of the operative field showing the adhesions about the forceps, caused by the introduction of an infected sponge.

an excellent field without undue strain. When all dissection has been completed and hemostasis has been attended to, the peritoneum is picked up with a row of forceps and stretched upward, and the edges are brought up close to each other. The preparation of the fluid in the meantime has been accomplished by an assistant. Two methods may be followed in introducing the prepared solution into the abdominal cavity. The first method consists of connecting a catheter with the container of the solution and allowing it slowly to fill the abdominal cavity. The other method being used by me now consists of pouring from



Fig. 7 (rabbit 4).—Photograph of the operative field eight weeks after the introduction of a solution of sodium citrate and papain and separation of adhesions showing the absence of adhesions which had been caused by the introduction of an infected sponge

200 to 300 cc. of the fluid into the abdomen every few minutes until 1,500 cc. has been used. The important step is to cover all the abdominal organs with the fluid and to be able to draw the omentum over the abdominal contents. The closure of the peritoneum is effected by everting the edges so that no raw surface of the peritoneum points into the abdominal cavity. Each suture is back stitched and rolled so that when one is through there is a rolled water-proof suture line. The suture is tied in several places, and the peritoneal edges are held



Fig. 8 (rabbit 5).—Photograph of the operative field after treatment with a solution of sodium citrate and papain, and separation of the adhesions. Note the absence of massive adhesion formation.



Fig. 9 (rabbit 6).—Photograph of the operative field after treatment with a solution of sodium citrate and papain and separation of the adhesions showing the complete absence of adhesions which had been caused by the introduction of an infected sponge.

up so that no spilling is done; the other layers are sutured in the usual manner. Distention of the bowel postoperatively is guarded against by the administration of ten doses of pitressin and by constant gastric deflation for three days. Fluids should be supplied intravenously from 4,000 to 5,000 cc. in twenty-four hours by the drop method. No drastic cathartics should be given. On the fourth day 1 ounce of liquid petrolatum given morning and evening with a small enema the following morning usually produces evacuation of the bowel. I have noted that when considerable spilling of the fluid occurred outside of the abdominal cavity onto the wound, faulty healing resulted with a ventral hernia. There was no infection in any of my cases.¹⁸

EXPERIMENTAL STUDY

An experimental study was made on thirty-eight rabbits and thirty patients to determine the value of papain in the prevention of the reformation of intra-abdominal adhesions. The results in the rabbits are presented in table 1. A summary of the data on the thirty patients is presented in the following outline, and an analysis of the results obtained is given in table 2.

Status of patients treated with the solution:

No. with no or one previous operation.....	8
No. with two previous operations.....	9
No. with three previous operations.....	6
No. with four previous operations.....	4
No. with five or more previous operations.....	3
Total	30

Time elapsed since treatment:

Less than one year.....	8
Between one and two years.....	12
Between two or more years.....	8
Deaths.....	2
Total.....	30

18. Since reporting these cases, nine more may be added to this group with uniformly good results. The technic was somewhat changed in the cases of severe involvement, 25 mg. of papain being dissolved in 500 cc. of sodium citrate solution (one 50 cc. ampule of 2.5 per cent sodium citrate was dissolved in 500 cc. of distilled water).

Sex:

Male.....	4
Female.....	26

Race:

Negro*.....	3
Others.....	27

* About 10 per cent, the same proportion as in population.

Results obtained:

Deaths.....	2
Poor results and fair.....	2
(One patient reoperated on and solution used again)	
Good clinical results verified by secondary operation and one by photograph and operation.....	2
(One patient reoperated on for hernia, photograph taken, and solution used again)	
(One patient reoperated on for hernia by another surgeon and reported by him to me)	
Good clinical results.....	22

A summary of the experiments on the animals follows: The mortality was 100 per cent when alcohol and ether were used to lavage the abdomen. When resection of the bowel was done a solution of papain had no influence on the ultimate course. The introduction of papain into the abdomen in the presence of gauze did not prevent formation of the adhesions, nor did it retard infection, the results being similar to those in the controls in which physiologic solution of sodium chloride alone was used. When papain in a solution of sodium citrate was used, the formation of adhesions was the least, and when adhesions formed they were very slight. From other experiments not reported here, I believe that a solution of sodium citrate alone has a mild action in preventing experimental formation of adhesions.

All told, there were thirty-eight rabbits on which forty-four operations were performed, with twenty deaths. Most of the rabbits had been previously used for routine laboratory experiments. The death rate was especially high in the controls. Papain in a solution of sodium citrate had a decided influence in the prevention of adhesions and mortality, being seemingly more effectual than any other substance used in these experiments.

TABLE 1.—*Results of Experiments on Rabbits*

Operation	Solution Used	No. of Animals	Recovery	Died	Postmortem or Operative Picture
Irritation; seraping; plus sponges	Physiologic solution of sodium chloride	3	0	3 (4th to 6th day)	Operative picture: frank pus around sponges, many adhesions, distention of bowel and spreading peritonitis
Irritation; seraping; application of tincture of iodine	Sodium citrate; papain	6	6	0	Operative picture: reoperated on at intervals of from 10 to 60 days; no adhesions in four animals; thin scattered adhesions in two; whitish plaques covered the viscera and parietal peritoneum, becoming dimpled in the longer interval
Irritation; seraping; application of tincture of iodine	Physiologic solution of sodium chloride	3	2	(4th day)	Postmortem picture: distention of abdomen; bowel adherent to wound Operative picture: two animals that lived reoperated on; moderate adhesions
Reoperated on; adhesions divided	Papain; sodium citrate	2	2	0	Operative picture: reoperated on three weeks later; abdomen free from adhesions
Irritation; seraping; application of tincture of iodine	Distilled water; papain	3	3	0	Operative picture: reoperated on on 12th day; all had fairly firm adhesions
Division of adhesions	Sodium citrate; papain	3	2	1 (1st day)	Postmortem picture: abdomen filled with bloody serum Operative picture: two animals that lived reoperated on on 20th day; moderate adhesions of bowel to wound
Irritation; seraping; application of tincture of iodine	Sodium citrate	5	4	1 (3d day)	Postmortem picture: firm adhesions of bowel to wound; distention Operative picture: four animals that lived reoperated on in three weeks; no adhesions in one; firm, generalized adhesions in three
Irritation; seraping; application of tincture of iodine; resection of bowel	Sodium citrate; papain, 1:25,000	3	0	3 (3d day)	Nothing found at autopsy
Irritation; resection of bowel	None	3	0	3 (1st day)	Nothing found at autopsy
Irritation; seraping; application of tincture of iodine	70% alcohol lavage	3	0	3 (next day)	Postmortem picture: peritoneum appeared red and flaxy; serosanguineous fluid found
Irritation; seraping; application of tincture of iodine	Lavaged with ether	3	0	3 (on table)	No cause of death found
Irritation and seraping plus gauze sponge	None	3	1	2 (4th day)	Postmortem picture: distention of bowel; generalized peritonitis; many firm adhesions Operative picture: animal that recovered had adhesions; bowel firmly adherent to sponge
Reoperated on; sponge removed; four weeks later reoperated on	Sodium citrate; papain	1	1	0	Operative picture: no adhesions found; peritoneum studded with whitish flakes
Irritation; seraping plus sponge left in	Sodium citrate; papain	3	3	0	Operative picture: reoperated on 4th day; moderate adhesions; serous fluid somewhat bloody; smear showed infection with colon bacilli; culture showed gas-producing organism

TABLE 2.—*Experimental Study of Thirty Patients on Basis of Results*

Patient, Date and Age	Previous Operations; Condition of Scars	Symptoms and Signs	DEATH	Operative Findings	Results
M. I. 9/19/32 17 yr.	One pelvic operation; gangrenous Meckel's diverticulitis; enterostomy; scars taut and red	Pain in lower portion of abdomen; vomiting; frequent colics, necessitating loss of work; painful scars; weight 81 pounds (36.7 Kg.); condition very poor		Few strong adhesions in lower portion of abdomen; cecum especially bound down; adhesions divided; 250 cc. of papain in physiologic solution of sodium chloride administered; patient did poorly and was uncooperative; pulled stomach tube out; gastrotomy performed for acute gastric dilatation on 9/26/33, under tri-bromethanol anesthesia *	Died 9/30/32, two weeks after operative procedure; autopsy showed acute gastric dilatation, raw areas over bowel in right quadrant and absence of adhesions
L. L. 2/6/35 49 yr.	Cholecystectomy and appendectomy, hysterectomy; division of adhesions ten days prior to last operation by another surgeon	Vomiting, moderate distention and pain in abdomen; poor results with enema and posterior pituitary after division of many adhesions, which were thick and numerous, according to description of operating surgeon; patient's condition poor		Very thick adhesions reformed in 14 days, hindering small bowels in one mass and adherent as a whole to last incision; separation of adhesions made through old incision; reformed adhesions were hard and very thick, requiring dissection with knife; 1,500 cc. of papain in sodium citrate solution administered	Died two days after operation; autopsy showed many old adhesions, perforation of bowel and inflammation of the ileum and marked fibrosis of the liver
A. S. 4/11/34 56 yr.	Suspension; hysterectomy; removal of adnexa; division of adhesions; thick scars and suprapubic hernia	Constant pain in scars and abdomen; peritoneal distention and colicky pains; weight 85 pounds (38.6 Kg.)	POOR AND FAIR RESULTS	Massive adhesions; sigmoid adherent to cecum; constriction of right ureter; right kidney enlarged; separation of adhesions and freeing ureter; 500 cc. of papain in physiologic solution of sodium chloride administered; tri-bromethanol anesthesia used	Poor; patient kept on complaining and having symptoms
Reoperated on 9/23/34	Same as in A. S.; recurrent hernia	Same as in A. S.		Adhesions much less; fistulous opening from cervix into abdomen; removal of cervix; 1,500 cc. of papain in distilled water administered; repair of hernia; adhesions divided; tri-bromethanol anesthesia used	Fair; somewhat better; still not well
M. I. 6/12/34 36 yr.	Hysterectomy, cholecystectomy and appendectomy; two thyroid operations; scars thick and keloid	Constant pain in left lower abdominal quadrant; constant pain in region of gallbladder; peritoneal obstruction; loss of weight		Massive adhesions in region of gallbladder and left lower abdominal quadrant; left ovary cystic, encased in adhesions; ovary removed and adhesions separated; 1,500 cc. of papain in sodium citrate administered; tri-bromethanol and general anesthesia used	Improved; gained weight; still complaints of soreness in lower part of abdomen, but none in the region of the gallbladder.
A. B. 5/29/34 44 yr.	Suspension; cholecystectomy; appendectomy; pelvic operation; exploration; scars moderately thick and recrossed	General abdominal pain, vomiting, constipation, diarrhea and colic; lost 20 pounds (9.1 Kg.); suprapubic postoperative hernia		Massive localized adhesions; opening sharply segregated in locale of surgical intervention; old median scar resected; removal of adnexa and supravaginal hysterectomy; 1,500 cc. of papain in sodium citrate solution administered; tri-bromethanol anesthesia used	Comment: It is noteworthy that in the area where a small mole was removed from the right thigh, the scar healed with a thick indurated base Improved; has some complaints; vague in character; no colic; improvement slow but steady

* Tri-bromethanol in amyloene hydrate was the form of anesthetic used when tri-bromethanol anesthesia is mentioned.

TWO PATIENTS OPERATED ON; ONE PHOTOGRAPHED

Mc. C. 3/24/34 32 yr.	Operations on pelvis, gallbladder and appendix; suprapubic keloid scars; postoperative hernia	Very obese; protruding hernia; signs of partial obstruction of bowel; vomiting with diarrhea; abdominal distention; dull aching pain in right lower quadrant; region of scars very painful	Large intraligamentous cyst on right side; many adhesions, thick and constricting; one loop of bowel tightly held in adhesions; resection of old suprapubic scar; resection of cyst; resection of sac and repair of hernia; 1,000 cc. of papain in sodium citrate solution administered; spinal anesthesia used	Reoperated on on 3/27/35, with following report: ventral hernia with several loops of bowel and omentum on the abdominal fascia; exploration of abdominal cavity showed no adhesions to intestines or adjacent viscera
W. E. 2/9/34 24 yr.	Suprapubic hysterectomy; appendectomy; resection of bowel; separation of adhesions; two scars in lower part of abdomen, one scar widened out, and hernia	Vomiting of three days' duration; no bowel movement; moderate distention; postoperative ventral hernia protruding	Ventral hernia; bowel adherent to sac; no gangrene; intestines marked firmly throughout abdomen; moderate distention; careful dissection of adhesions; resection of sac and freeing of herniated bowel; papain in sodium citrate solution; closure	Clinically good; patient reentered hospital 11/26/34 for repair of recurrent ventral hernia; photograph of abdominal contents taken showing abdomen free from adhesions
W. R. 3/11/32 41 yr.	Ruptured appendix; enormous keloid scar; one operation for adhesions	Acute obstruction of bowel; symptoms of chronic partial obstruction several years	Reoperated on 11/26/34; ventral hernia; 1,500 cc. of papain in sodium citrate solution administered	Good; no complaints
G. E. 3/19/32 29 yr.	Appendectomy three years ago; redrained operative field for adhesions	Acute obstruction of bowel; very obese; pregnant five months; ventral hernia; bulging not strangulated	Thick cartilaginous hands encircling part of ileum and many waves of adhesions; dissection of adhesions and invagination of injured small bowel; 1,500 cc. papain in physiologic solution of sodium chloride administered; spinal anesthesia used	Miscarriage; condition good; no complaints
M. C. 3/21/32 20 yr.	Four abdominal operations; scars thick and painful	Pain in abdomen; chronic obstruction with occasional exacerbation; very obese	Abdomen a complete mass of adhesions with many constricting bands; separation of adhesions; papain in physiologic solution of sodium chloride, 1,25,000, administered; spinal anesthesia used	Good; recovery slow
B. E. 5/31/32 35 yr.	Eight operations, including two or three intestinal resections; abdomen all scars	Acute intestinal obstruction; abdomen distended; vomiting; very ill	Massive adhesions; distal part of ileum adherent to midpubic incision; strangulated; left herniation of strangulated loop and separation of adhesions; 1,500 cc. of papain in physiologic solution of sodium chloride administered; spinal anesthesia used	Very good
P. K. 6/29/32 46 yr.	Two operations, gallbladder and pelvis; thick indurated scars	Pain; chronic obstruction; acute attacks	Thick ropelike adhesions in hepatic area and right lower quadrant; separation of adhesions; 1,500 cc. of papain in physiologic solution of sodium chloride administered; spinal anesthesia used	Good

Comment: This patient had papain twice with excellent clinical results

RESULTS

TABLE 2.—*Experimental Study of Thirty Patients on Basis of Results—Continued*

Patient, Date and Age	Previous Operations; Condition of Scars	Symptoms and Signs	Operative Findings	Results
J. M. 7/28/32 31 yr.	Two operations; thick scars	Generalized abdominal pain; acute exacerbation of chronic abdominal pain; vomiting; mod- erate distention	Resection of mldrppable scar; obstruction of terminal ileum field; adhesions sepa- rated; 1,500 cc. of papain in physiologic solution of sodium chloride administered; spinal anesthesia used	Good
W. M. 9/18/32 42 yr.	Two operations, one for obstruc- tion of bowel	Abdominal pain in region of scars; distention and vomiting; small particles of feces; emaciated	Ropelike adhesions in lower part of abdo- men; retrocecal appendix; cecum adherent to wound; appendectomy and separation of adhesions; 1,500 cc. of papain in physio- logic solution of sodium chloride adminis- tered; spinal anesthesia used	Good
W. B. 10/9/33 34 yr.	Two operations, one for adhe- sions with obstruction of bowel; keloid scars	Acute obstruction of bowel; exacerbation of chronic abdom- inal condition	Ileum obstructed by bands of adhesions; abdomen full of waves of adhesions; resection of loop of ileum; 1,500 cc. of papain in physiologic solution of sodium chloride administered; spinal anesthesia used	Good
S. A. 1/15/34 39 yr.	One operation, vaginal hyster- ectomy; no scar	Chronic abdominal pain, acute attacks entering in pelvic region; bloating	Many adhesions in pelvic abdomen; sig- moid and cecum adherent to stump; right oophorectomy, appendectomy and separa- tion of adhesions; 1,500 cc. of papain in sodium citrate solution administered; spinal anesthesia used	Good
G. R. 3/19/34 26 yr.	One operation; thick scar	Chronic abdominal condition for two years; loss of weight; bloat- ing	Emmeshed uterus; adnexa removed previ- ously; frozen pelvis; sigmoid adherent to scar; hysterectomy and separation of adhe- sions; 1,500 cc. of papain in sodium citrate solution administered; spinal anesthesia used	Good
F. M. 3/23/34 29 yr.	One operation; normal appear- ing scar	Constant pain in lower part of abdomen; two acute attacks diagnosed as obstruction of bowel relieved by medical treatment	Uterus frozen in mass of adhesions; both tubes emmeshed; right salpingo-oophorec- tomy, left salpingectomy, suspension and separation of adhesions; 1,500 cc. of papain in sodium citrate solution administered; tri-bromethanol anesthesia used	Patient developed mental symptoms; abdominal condition good; psychosis cleared up
T. S. 3/26/34 18 yr. male	One operation; thick scar	Constant pain in lower part of abdomen following appendectomy two months before; bowel move- ments possible but difficult; emaciated	Mass of adhesions in iliocecal region; dis- section of large bowel; division of adhe- sions and exploration; 1,500 cc. of papain in sodium citrate solution administered; tri-bromethanol anesthesia used	Good
S. G. 4/2/34 26 yr.	No operations	Generalized abdominal pain; obstipation; frequent colicky attacks, with diarrhea and abdominal distention	Abdomen filled with adhesions in region of gallbladder between liver and parietal peri- toneum, lower part of abdomen and pelvis; separation of adhesions, appendectomy and plastic operation on both adnexa; 1,500 cc. of papain in sodium citrate solution admin- istered, gas and ether anesthesia used	Good all over abdomen; moderate amount of tenderness in region of gallbladder

B. J. 6/10/34 56 yr.	Two operations; postoperative ventral hernia scar widened; very obese	Increasing difficulty in defecation, with pain in lower part of abdomen during defecation; distention, occasional strangulation in hernia reducible	Massive adhesions involving distal and descending colon; adhesions from one side adherent; separation of loops of bowel in hernia; 1,000 cc. of papain in sodium citrate solution administered; tri-bromethanol anesthesia used	Good; no complaints
R. L. 5/10/34 44 yr.	Five operations, two ventral hernias; postoperative scars thin and stretched out in other adhesions; radium treatments to cervix	Strangulation of bowel while straining at stools; constant abdominal pains; partial bowel obstruction several times; diarrhea and constipation	Two hernial protrusions, masses of adhesions around hernias and region of gall bladder; resection of scars at hernia, separation of adhesions and repair of hernia; papain in sodium citrate solution administered; tri-bromethanol anesthesia used	Good
S. L. 7/30/34 27 yr.	Appendectomy; scar widened	Pain in area of operation and scar; vomiting and distention; emaciation	Area of scar contains many adhesions; cecum adherent to scar; left ovary cystic; right salpingo-oophorectomy and separation of adhesions; papain in sodium citrate solution administered; tri-bromethanol anesthesia used	Good
O. E. 8/14/34 30 yr.	Three operations; hernia, two scars only being present	Pain in lower part of abdomen; chronic and boring; distention; obstipation; emaciated	Postoperative ventral hernia, many intra-abdominal adhesions involving small and large bowel; separation of adhesions and removal of left ovarian cyst; papain in sodium citrate solution administered; tri-bromethanol anesthesia used	Good
M. A. 9/25/34 22 yr.	Three operations, one ileostomy for obstruction; postoperative ventral hernia; scars thick	Pain in region of scars; intestinal obstruction three times; operated on once; distention periodic	Many adhesions; hernia encased in adhesions; resection of median scar, separation of adhesions and repair of hernia; papain in sodium citrate solution administered; spinal anesthesia used	Good
M. O. 9/23/34 33 yr.	One operation; ruptured gastric ulcer; enterostomy; scar thin	Acute obstruction of bowel	Adhesions at site of enterostomy; loop of pyloric region; re-are of obstruction in separation of adhesions; 1,500 cc. of papain in sodium citrate solution administered; Massive adhesions in appendiceal region and pelvis, also in region of left colon; separation of adhesions; 1,500 cc. of papain in sodium citrate solution administered; tri-bromethanol anesthesia used	Good
F. V. 1/7/35 21 yr.	Operations, for appendicitis; pelvic condition and obstruction of bowel; wide thick scar	Constant pain in lower part of abdomen; acute attacks, relieved by medical means; obstipation and diarrhea; considerable loss of weight	Comment: Patient complained of pain on defecation for three or four weeks; feels good now	Good
S. O. 5/1/35 20 yr.	Two operations, appendectomy and exploratory for intestinal hemorrhoids	Severe pain in whole abdomen; cramps and vomiting; massive hemorrhages from bowel	Massive adhesions involving whole of abdomen; loops of bowel adherent to scar and omentum; separation of adhesions; 1,500 cc. of papain in sodium citrate solution administered; tri-bromethanol anesthesia	Undetermined; immediate result good

SUMMARY AND CONCLUSION

A study of intra-abdominal adhesions based on the experimental findings in thirty-eight rabbits and thirty human patients is presented. This study was made with papain, standardized and prepared according to the method of Ochsner and Walton, by Parke, Davis & Co. The earlier works of Walton, Kubota and others were freely consulted.

In the experimental and clinical cases presented, I found that a solution of 0.08 per cent sodium citrate in distilled water in which 25 mg. of papain is dissolved makes a satisfactory solution. I believe that sodium citrate has a synergistic action with papain.

All the earlier work on the prevention of the reformation of intra-abdominal adhesions was built on the theory that a mechanical lubricant would stop the natural process of production of fibrin and fibrous tissue or stop the phenomenon of natural defense.¹⁴ The method herein described is based on the response of the defense mechanism, the solution acting directly on the fibrin, preventing the formation of the end-product in diverting the process of peritoneal reaction to a digestion of the fibrin formed. Thirty clinical cases are cited in which a solution of papain was used. In two cases death occurred which could not be attributed to the drug used; in two the results were poor and in twenty-six they ranged from good to excellent.

DIFFERENTIAL ANALYSIS OF BILE ACIDS IN HUMAN BILE FROM FISTULAS

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In a previous communication¹ the differential bile acid analysis of a large series of samples of bile removed from gallbladders at operation was reported. The bile was analyzed for bile acids conjugated with taurine and with amino-acetic acid, for cholic acid, for desoxycholic acid and for free bile acids. It was shown that the point of greatest significance was the variation in the proportions of the different bile acids in any one sample. Thus, in samples of bile removed from normal gallbladders, cholic acid formed about one half of the total bile acid content, while about 20 per cent of the total was in the form of free bile acids. In cases of chronic cholecystitis, the cholic acid content averaged about 30 per cent and the free bile acid content about one third of the total bile acid content. In sharp contrast, analysis of the bile from the gallbladder in cases of acute cholecystitis revealed that the cholic acid content averaged about one sixth and the free bile acid content about 50 per cent of the total bile acid content. The total bile acid content in cases of acute cholecystitis averaged about one fourth of that in cases of chronic cholecystitis. The fall in the ratio of cholic acid and the rise in the relative percentage of free bile acids were apparently due to the fact that the various bile acids were absorbed in a differential manner by the inflamed wall of the gallbladder.

In several cases, however, in which the gallbladder was found to be practically normal, marked variations in the bile acids were noted. These variations were thought to be due to pathologic changes in the liver. That the liver can secrete the various bile acids in abnormal proportions has already been noted by Andrews and his co-workers.² It seemed, therefore, to be of some importance to utilize the method of differential bile acid analysis in investigating the direct secretion of

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1. Colp, R., and Doubilet, H.: Differential Analysis of Bile Acids in Human Gallbladder Bile, *Arch. Surg.* **33**:913 (Dec.) 1936.

2. Andrews, E.; Hrdina, L., and Dostal, L. E.: Etiology of Gallstones: II. Analysis of Duct Bile from Diseased Livers, *Arch. Surg.* **25**:1081 (Dec.) 1932.

the liver in cases of drainage from a fistula in human beings. The strong influence of the gallbladder could thus be excluded, except in a fistula of the type seen after cholecystostomy. It is evident that such an investigation might be of great value in studying the etiologic factors and the underlying mechanisms involved in the different pathologic conditions of the liver and biliary tract.

METHOD

The method for the differential bile acid analysis has been previously described. All determinations were carried out in duplicate. In general, 5 cc. of bile from the fistula was extracted with 80 cc. of boiling 95 per cent alcohol, and the method of Schmidt and Dart used to determine the bile acids conjugated with taurine and with amino-acetic acid. Depending on the apparent concentration of the bile, from 15 to 40 cc. of bile was precipitated with zinc hydroxide, and the clear bile salt extract was used to determine both the cholic acid by a modification of the procedure of Gregory and Pascoe (colorimetric) and the total bile acids by an iron precipitation method. The percentage of free bile acid was estimated by subtracting the conjugated bile acids from the total bile acids. The bile acids, expressed as deoxycholic acid, also included, of course, the small amounts of anthropodeoxycholic and lithocholic acids present in human bile in small amounts. The figures for the total bile acid content do not include the weight of the conjugated taurine and amino-acetic acid, since the percentages are calculated on the basis of the hydrolyzed bile acids.

MATERIAL

Bile drained from a fistula in twenty-seven human patients was analyzed either on consecutive days after operation or on every second or third day. As a rule, since in most cases bile entered the intestinal tract to some extent, quantitative studies could not be carried out.

The cases may be conveniently summarized under three divisions.

I. Release of complete or incomplete obstruction (17 cases)

A. Complete obstruction (2 cases)

1. Chronic pancreatitis (case 1)
2. Carcinoma of the head of the pancreas (case 2)

B. Incomplete obstruction (15 cases)

1. Without stone (cases 3 and 4)
2. Calculi of the choledochus (cases 5 to 11)
3. Stricture (case 12)
4. Pancreatitis (cases 13 to 17)

II. Cholangitis and cholangiolitis (7 cases)

Cases 18 to 24

III. Hepatitis (3 cases)

Cases 25, 26 and 27.

Few of the cases fall completely under any one heading, since a considerable amount of cholangitis was noted in many of the cases of stone in the choledochus, while in a number of cases cholangitis was associated with stones in the common duct. In one case hepatitis was associated with acute cholangiolitis.

RESULTS

Group I.—Cases of complete or incomplete biliary obstruction.

CASE 1.—G. H., a man aged 44, was first admitted to the hospital on Feb. 18, 1933, with a diagnosis of acute pancreatitis. He gave a previous history of attacks of heartburn for four years, associated with epigastric fulness and mild pain. Cholecystostomy was performed. The fistula drained for three months before closing. The patient was well, except for one attack of epigastric pain, until May 1934, when the attack recurred accompanied by jaundice. Operation was performed again on Feb. 13, 1934. The liver was found to be enlarged and somewhat firm. The gallbladder was not distended but showed subacute inflammation and contained rather pale, thin bile with many flocculi. There were several large, acutely inflamed lymph glands alongside the cystic duct. The choledochus was

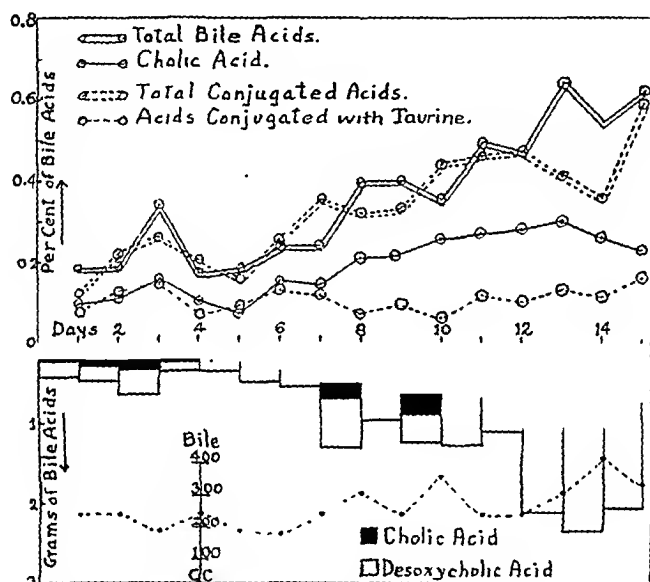


Chart 1 (case 1).—Chart showing the results of bile acids analysis after the release of complete obstruction due to chronic pancreatitis. Note the gradual steady increase both in the volume of bile and in the percentage of bile acids; the percentage of cholic acids to the total bile acids, which remains persistently about 50 per cent; the intermittent high false figures for the total conjugated bile acids, and the relatively slow increase in the taurine-conjugated bile acids.

twice the normal size and contained pale greenish bile. The entire pancreas was hard, irregular and indurated and larger than normal. A diagnosis of chronic pancreatitis with biliary obstruction was made.

Cholecystectomy and drainage of the common duct were performed. All the bile drained through the fistula. Urobilin was persistently absent from the stools. The patient was discharged with a complete biliary fistula.

The results of the analysis of bile (chart 1) exemplify clearly the recovery of bile acid by the liver after complete obstruction in the absence of an infection and without refeeding the bile. The percentage of bile acids gradually rose from 0.18 on the first day to 0.62 on the fifteenth day. The percentage of cholic acid tended to stay at about one-half that of the total bile acid content. The conjugated bile

acids formed a criss-cross pattern with the total bile acids. Apparently in the recovery phase some unknown material, probably derived from an exudate, is present in the bile. This material is soluble in alcohol and yields nonbile acid aminonitrogen. This aminonitrogen cannot be separated from the aminonitrogen released by the taurine and amino-acetic acid and so is included in the calculation for the conjugated bile acids. Consequently the calculated result yields a figure higher than the total bile acids. As the bile approached normality on the eleventh day, this excess disappeared. Especially to be noted is the relatively slow increase in taurine bile acids. By the fourteenth day the bile acids were in their normal proportions. The cholic acid content was about half the total bile acid content; the taurine bile acid content was about equal in proportion to the bile acids combined with amino-acetic acid, and a little over 20 per cent of the total bile acid content was nonconjugated. The volume of bile excreted gradually rose from 240 to 330 cc. As a result, the total amount of bile acid excreted rose from a little less than 0.5 Gm. to over 2 Gm. Daily.

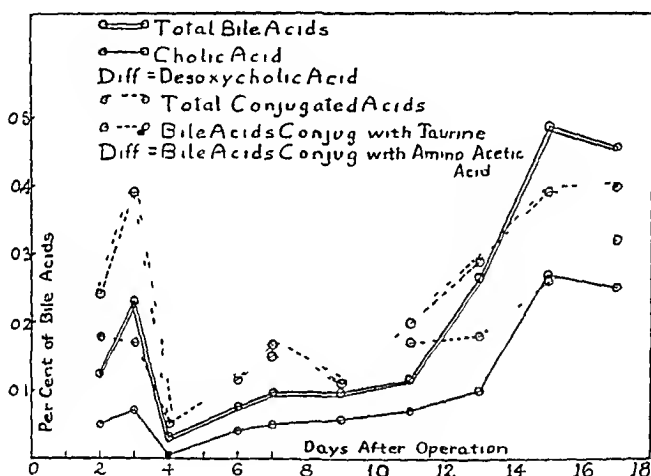


Chart 2 (case 2) —Curves showing the results of bile acid analysis in a case in which cholecystostomy was done for complete obstruction due to carcinoma of head of pancreas. Note the percentage of cholic acid, which remains persistently about 50 per cent of the total bile acid content; the high false results for conjugated bile acids up to the thirteenth day, and the sudden drop in the percentage of bile acids on the fourth day

CASE 2—S. E., a housewife aged 58, on admission to the hospital gave a history of occasional dull pain in the right upper quadrant of the abdomen of two years' duration, a history of polydipsia, polyuria and glycosuria of six months' duration and the loss of 55 pounds (24.9 Kg.) in weight. Three weeks before operation, jaundice, light colored stools and dark urine developed. On her admission to the hospital, the edge of the liver was 7 cm. below the costal margin, the stools contained a trace of urobilin, the icteric index was 130 and the bilirubin content of the blood was 5 mg per hundred cubic centimeters. The urine contained 3.5 per cent sugar. At operation the gallbladder was found to be subacutely inflamed and distended and to contain whitish bile and one large and several smaller cholesterol stones. The choledochus was greatly distended. Carcinoma of the head of the pancreas was found. Owing to the presence of inflammation, chole-

cystostomy only was performed. After three weeks the patient was discharged to the care of her physician.

The results of the analyses of the bile for bile acids in this case, in which complete drainage occurred through a fistula in the gallbladder, are summarized in chart 2. The sudden drop in the percentage of bile acids on the fourth day is to be noted. The percentage of bile acids gradually increased from 0.03 per cent on the fourth day to 0.45 per cent on the seventeenth day. The method of Schmidt and Dart yielded high false results up to the thirteenth day; when the percentage of total conjugated bile acids was low, from the fourth to the ninth day, the taurine bile acids, as determined from the sulfur present, masked any bile acids conjugated with amino-acetic acid that may have been present. The cholic acid content tended to maintain its ratio of 50 per cent of the total bile acid content throughout. By the fifteenth day, the proportions of the different bile acids were normal, the cholic acid forming half of the total bile acid and the conjugated

TABLE 1.—*Output of Bile Acids After Relief of Obstruction in Case 2*
(Complete Diversion of Bile)

Days After Operation	Volume of Bile, Cc.	Total Bile Acids, Percentage	Total Bile Acid Output, Gm.
2...	1,020	0.12	1.22
3...	1,620	0.23	3.72
4...	1,200	0.03	0.36
5..	1,260
6..	960	0.08	0.77
7..	810	0.10	0.81
8..	1,380
9..	1,380	0.10	1.38
10..	1,040
11..	600	0.11	0.66
12..	570
13..	480	0.27	1.29
14..	360
15..	540	0.48	2.59
16..	360
17...	540	0.46	2.48

acids four fifths of the total while the taurine bile acids were equal in proportion to the amino-acetic bile acids.

Chart 2 illustrates clearly the fallacy of using any one method for the analysis of bile acid. Thus, if the method of Schmidt and Dart alone were used, the results would be too high up to the thirteenth day and too low beyond that. By the employment of the method of Gregory and Paseoe, since it measures only cholic acid, not only would half of the total bile acids be missed, but owing to lack of sensitivity, no color would be registered up to the thirteenth day, when the percentage of cholic acid first rose to 0.01.

On analyzing the daily volume output of bile in this case (table 1), one is struck by the marked cholerrhagia during the first week. This type of severe reaction of the liver to obstruction has been noted by others.~ The output of 3.72 Gm. of bile acids on the third day is especially to be noted

3. Walters, W., and Parham, D.: Renal and Hepatic Insufficiency in Obstructive Jaundice, Surg., Gynec. & Obst. **35**:605 (Nov.) 1922. Bergareche, J. La colerragia postoperatoria, signo externo de la insuficiencia hepática, Arch. de med. cir. y especialid. **36**:189 (Feb 18) 1933.

CASE 3.—M. F., a woman aged 50, had a cholecystectomy performed in 1929, after a history of disease of the gallbladder and diabetes of fifteen years' duration. She was well, except for the diabetes, for four years, when the attacks of epigastric pain recurred. At operation on Feb. 21, 1934, the common bile duct was found dilated to twice the normal size, and the liver was large, with rounded edges. No stones were found. The pancreas seemed slightly harder than normal. A biopsy of the liver showed nothing abnormal. The patient died six days after choledochostomy, with a temperature of 104. F. Autopsy was not performed.

TABLE 2.—*Differential Bile Acid Analysis of Bile from a Fistula in Various Conditions*

Case No.	Days After Operation	Bile Acids Conjugated with		Total Bile Acids Conjugated	Cholic Acid	Desoxycholic Acid	Total Bile Acids	Cholic Acid, Percentage	Free Bile Acid, Percentage	Comment
		Tau- rine	Amino- Acetic Acid							
3	2	0.23	0.04	0.32	0.10	0.14	0.24	42	..	Intermittent obstruction without jaundice or infection; biliary drainage; 2d day 660 cc.; 3d day, 1,260 cc.; 4th day, 1,260 cc.
	3	0.23	0.21	0.49	0.08	0.40	0.48	17	..	
	4	0.20	0.09	0.29	0.22	0.13	0.35	62	17	
4	8	0.24	0.17	0.41	0.27	0.30	0.57	47	29	Drainage from cystic duct after acute cholecystitis
5	3	0.19	0.18	0.37	52	..	Stone in choledochus without infection or jaundice
	9	0.09	0.11	0.20	45	..	
9	1	0.25	0.00	0.25	0.17	0.07	0.24	70	..	Stone in common bile duct, associated with jaundice
	3	0.21	0.00	0.21	0.05	0.20	0.25	20	16	
	4	0.12	0.00	0.12	0.04	0.04	0.08	50	..	
10	2	0.20	0.23	0.43	0.07	0.22	0.29	24	..	Ten yr. after cholecystectomy; stones in common duct without infection; slight jaundice
	4	0.15	0.01	0.16	0.04	0.04	0.08	50	..	
	5	0.11	0.00	0.11	0.03	0.00	0.03	100	..	
	7	0.07	0.04	0.11	0.04	0.01	0.05	80	..	
11	1	0.13	0.13	0.26	0.08	0.21	0.29	27	10	Hydrohepatosis; stones in choledochus with marked acute obstruction and jaundice
	5	0.10	0.00	0.10	0.03	0.00	0.03	100	..	
	9	0.05	0.00	0.05	0.03	0.04	0.12	66	54	
13	15	0.25	0.80	1.05	0.63	0.45	1.08	58	3	Drainage from cystic duct after acute cholecystitis, associated with jaundice and enlarged pancreas

Analysis of the bile acids (table 2) revealed that on the second day the cholic acid content was 42 per cent of the total bile acid content, while on the third day the ratio had fallen to 17 per cent. On both these days, however, the conjugated bile acid content was higher than the total bile acid content. On the fifth day, the percentage of cholic acid had risen to 62, and the percentage of free bile acids was 19. There was definite evidence of cholerrhagia, since the liver excreted 1,260 cc. on the third and fifth days. The cause of death, except for the indefinite diagnosis of "liver death," was not discovered.

CASE 4.—In this case cholecystectomy was performed for acute cholecystitis. The cystic duct was drained. On the eighth day, when the bile was probably normal, the cholic acid content was 47 per cent of the total bile acid content and the free bile acid content was 29 per cent of the total. The percentage of total bile acids was rather low (table 2).

CASE 5.—H. N., a housewife aged 38, was subjected to cholecystectomy in 1931 for relief from symptoms which had been present for nine years. These consisted essentially of frequent attacks of severe persistent epigastric pain, radiating to both the right and the left upper quadrant of the abdomen, to the back and to both scapulae, occurring two hours after meals and lasting from one to three hours. At operation a somewhat diseased gallbladder, containing a large number of small faceted stones, was removed. The patient was well for eleven months, when the attacks of epigastric pain recurred, unchanged except that on one occasion jaundice was present. Eighteen months after the first operation choledochostomy was performed; nothing was found to explain the symptoms. As soon as the biliary fistula closed, the attacks recurred. The patient was admitted to this hospital on June 17, 1933. All investigations gave negative results, and she was allowed to return home. After prolonged observation it was felt that the symptoms could be explained most easily by the presence of a calculus too small to cause complete obstruction or even temporary jaundice.

At operation on December 1 a small faceted calculus was found in the retro-duodenal portion of the choledochus, which was not dilated. The stone was removed, and choledochostomy was performed. Convalescence was uneventful, and the patient has been well since. Analysis of two samples of the bile drained from the fistula (table 2) revealed that the cholic acid content was 52 and 45 per cent of the total bile acid content. It is to be noted that the total bile acid content was rather low, even on the ninth day.

CASE 6.—H. S., a white man aged 57, gave a history of four attacks of epigastric pain, radiating to the right upper quadrant of the abdomen and to both scapulae, during the past year. The last attack occurred twenty days before operation. Seven days later jaundice was noted. On admission, the liver was large. Bile was present in the stools and in the duodenum. The icteric index was 90. At operation on Sept. 20, 1935, the gallbladder was found thickened and distended, but it contained no stones. The choledochus was slightly dilated and contained one large stone. A probe passed easily into the duodenum. Choledochostomy was performed. The patient has been well since his discharge.

The bile acid analysis of the bile drained from the fistula (chart 3) revealed definite abnormalities. The bile drained the first day contained almost 1 per cent of bile acids, which was practically all free desoxycholic acid. The conjugated bile acid content remained low, while the cholic acid was present only in traces. The decrease in the percentage of bile acids on the fifth day is to be noted. By the tenth day, the concentration of total bile acids was slightly below 0.40 per cent, being somewhat similar to the concentration noted in cases 1 and 2 on the corresponding day.

CASE 7.—C. F., a housewife aged 60, had had attacks of gallbladder pain for five years. With the last attack, twelve days before operation, jaundice was noted. The icteric index was 50, and the bilirubin content of the blood, 2 mg. per hundred cubic centimeters. At operation the gallbladder was found to be full of stones and acutely inflamed. The common bile duct was twice the normal diameter, thickened, inflamed and full of a sandlike precipitate, but contained no stones. Cholecystostomy and choledochostomy were performed. There was evi-

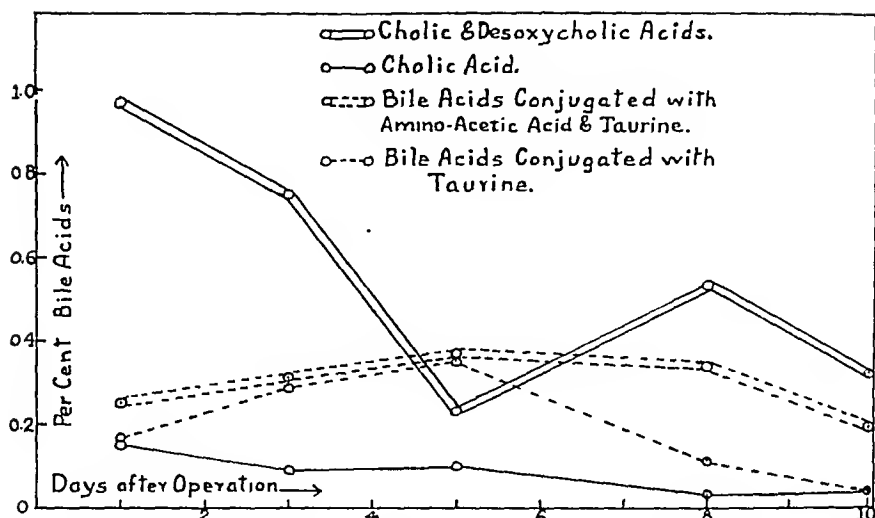


Chart 3 (case 6).—Chart showing the results of bile acid analysis in a case of intermittent obstruction of one years' duration due to a stone in the choledochus. Note the high percentage of free desoxycholic acid, the almost complete absence of cholic acid and the fall in the concentration of bile acids on the fifth day.

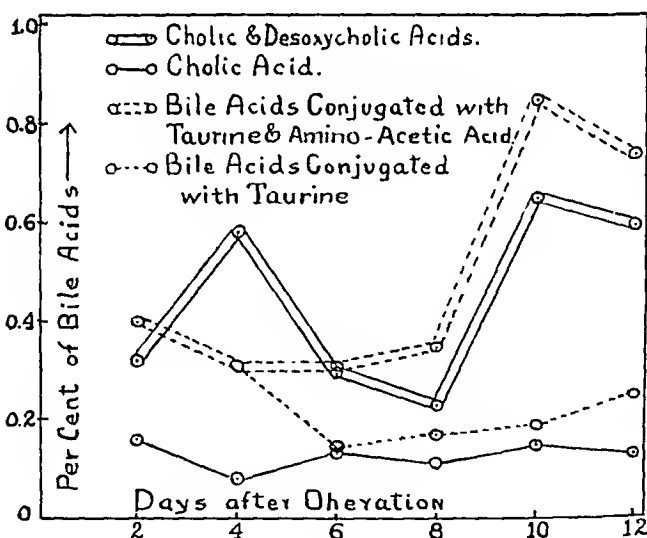


Chart 4 (case 7).—Chart showing the results of bile acid analysis in a case of acute cholecystitis, choledochitis and cholelithiasis with a sandlike precipitate in the common bile duct. Note the low ratio of cholic acid, associated with inflammation of the bile ducts, the fall in the concentration of bile acid on the eighth day as a result of excessive loss of bile through the fistula and the high false result for conjugated bile acids from the eighth day on. These false results were associated with the presence of pancreatic enzymes in the bile.

dent spasm of the sphincter of Oddi, the measurements of its resistance on the third and sixth days being 185 and 220 mm. of water. As a result, urobilin was not present in the stool until the nineteenth day.

A perusal of the bile acid analysis of the bile from the fistula (chart 4) showed a low ratio of cholic acid. To be especially noted is the excessively high false percentage of conjugated bile acids on the last six days of the analysis. During that period pancreatic enzymes were found in the bile from the fistula, apparently as a result of spasm of the sphincter of Oddi causing regurgitation of pancreatic juice.

CASE 8.—F. S., a housewife aged 61, had suffered from attacks of pain in the right upper quadrant of the abdomen for twenty years. With her last attack, twenty-four days before operation, jaundice developed. On her admission to the hospital the icteric index was 160, and the bilirubin content of the blood was 14 mg. per hundred cubic centimeters. While the patient was under observation

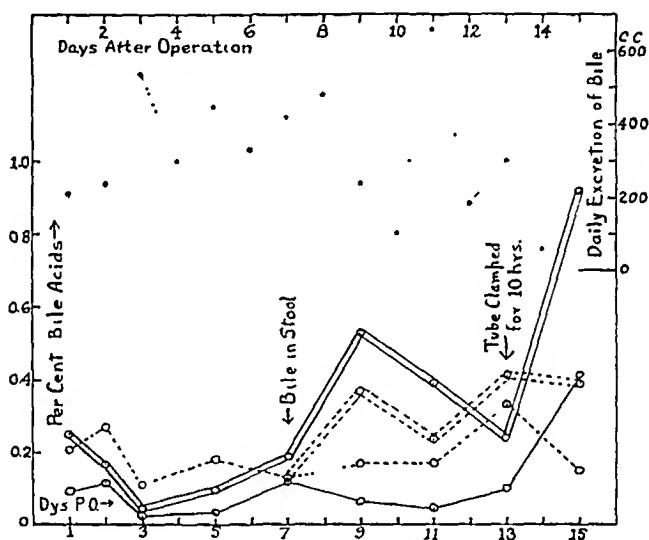


Chart 5 (case 8).—Chart showing the results of bile acid analysis in a case of chronic cholecystitis and cholelithiasis and stones in the choledochus associated with marked obstructive jaundice. Note the high false results for conjugated bile acids for the first five days, the drop in concentration on the third day, the drop in concentration on the thirteenth day following the loss of 660 cc. of bile on the previous day and the rise in the concentration of bile acids after the entrance of bile into the intestine. The various bile acids are beginning to approach their normal proportions on the fifteenth day.

the icteric index fell to 30. At operation the gallbladder was found to be thickened and full of stones. The common bile duct contained pigment stones and precipitated material and was dilated. Choledochostomy was performed. Urobilin was not found in the stool until the eighth day. The sphincter of Oddi was found to be spastic both by actual measurement and by studies made with the injection of iodized poppy-seed oil 40 per cent. On the thirteenth day after operation the tube was clamped, magnesium sulfate was given by mouth and the patient was atropinized. The next day the stool contained a large amount of bile. The tube was removed on the nineteenth day, and the patient has been well since

A study of the secretion of bile acids in the bile from the fistula (chart 5) is of great interest, especially when correlated with the volume of biliary excretion and with the presence of bile in the stool. It can be seen that the excretion of bile acids was very low during the first seven days. A typical drop occurred on the third day. There was an excessively high amount of conjugated bile acids during the first five days. On the ninth day after the appearance of bile in the stool there was a sudden rise in the concentration of bile acids. On the eleventh day, apparently due to recurrent spasm of the sphincter of Oddi, there was a loss of 660 cc. of bile through the fistula. The next day both the volume and the percentage concentration of the bile from the fistula dropped markedly. After the clamping of the tube and the appearance of large amounts of bile in the stool, the percentage of bile acids rose to 0.92. Associated with this was the sudden drop in the excretion of bile from the fistula due to the relaxation of the sphincter of the common duct.

This case is of great significance in that it shows clearly how the entry of bile into the intestinal tract sharply raises the concentration of bile acids in the bile. The results in chart 5 should be compared with the steady and slow rise in the concentration of bile acids shown in chart 1, in which case no bile entered the intestinal tract.

CASE 9.—B. S., a housewife aged 66, had suffered from diabetes for fifteen years. Eight weeks before operation she began to have attacks of biliary colic, associated apparently with slight jaundice. Two days before operation jaundice became marked, and fever was present. On her admission to the hospital the icteric index was 30, with a bilirubin content of the blood of 1.5 mg. per hundred cubic centimeters. At operation the gallbladder was found to be shrunken and to contain no stones. The choledochus was dilated and held a single large stone. Choledochostomy was performed. The tube was dislodged on the fourth day, but bile continued to drain for four weeks, up to the time of the patient's discharge. The fistula closed three weeks after discharge, and the patient has been well since. The prolonged drainage was apparently due to a spastic sphincter of the common duct, found to be so by actual measurement.

The bile from the fistula was analyzed for four days. The results (table 2) show a high proportion of cholic acid on the first day. By the third day the cholic acid content had fallen to 20 per cent, but on the fourth day it rose to 50 per cent.

CASE 10.—S. S., a woman aged 48, on whom cholecystectomy was performed ten years previously, was admitted to the hospital with a history of attacks of pressing epigastric pain, associated with jaundice, of two weeks' duration. There were no chills or fever. The stools were noted to be brown, but the urine was dark. On admission the icteric index was 12, and the bilirubin content of the blood was 0.5 mg. per hundred cubic centimeters. At operation the choledochus was three times the normal size and contained two stones, one in the retroduodenal portion. After removal of the stones, choledochostomy was performed.

The results of the analysis of the bile (table 2) are abnormal. Although the cholic acid content was low in proportion on the second day, on the fourth, fifth and seventh days it was 50, 100 and 80 per cent of the total bile acid content. In all these analyses it is to be noted in addition that the amount of conjugated acids was much higher than the total bile acids content.

CASE 11.—A case somewhat similar to case 10 was that of a 54 year old fireman (D. L.) who suffered from two severe attacks of epigastric pain, one six weeks and the other three weeks before operation. Jaundice was present

with the last attack. The icteric index was 85, and the bilirubin content of the blood was 7.5 mg. per hundred cubic centimeters. At operation the common bile duct was greatly distended and found to contain white bile and ten large stones. Choledochostomy was performed.

Analysis of the bile from the fistula (table 2) revealed that although the cholic acid content on the first day was only 27 per cent, on the fifth day it was 100 per cent and on the ninth day 66 per cent.

CASE 12.—T. R., a 35 year old woman, had undergone cholecystectomy six months previously at another hospital for symptoms of ten years' duration. It was noted that after the operation a biliary fistula persisted for ten weeks. Five months later painless jaundice developed. On her admission to the Mount Sinai Hospital the icteric index was 20, and the bilirubin content of the blood was 0.2 mg. per hundred cubic centimeters. Operation, performed twenty-five days

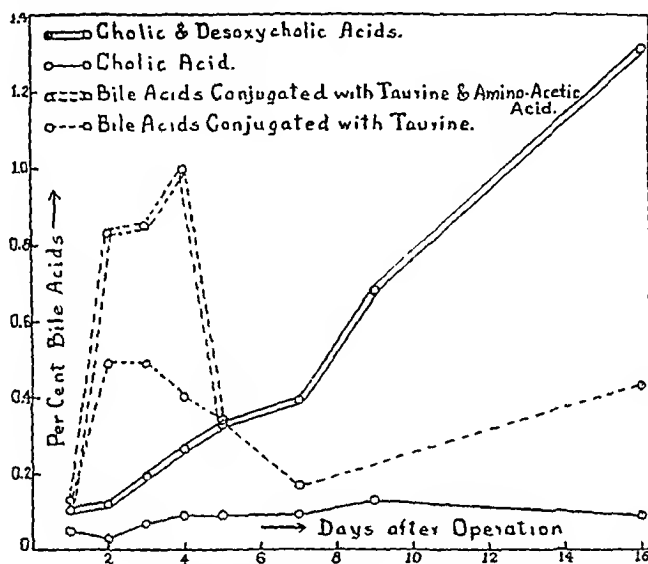


Chart 6 (case 12).—Chart showing the results of bile acid analysis in a case of stricture of the choledochus six months after cholecystectomy. Note the high false results for conjugated bile acids on the first four days, the high proportion of free desoxycholic acid, the presence of cholic acid only in traces and the presence of only taurine-conjugated bile acids after the fifth day.

after the onset of jaundice, revealed an almost complete stricture at the junction of the hepatic ducts. A tube placed in the hepatic ducts was used to achieve drainage.

Analysis of the bile (chart 6) obtained on drainage yielded abnormal results. Aside from the excessively high false results for conjugated bile acids the first four days, the extraordinary finding was the increasing excretion daily of free desoxycholic acid. Starting at 0.1 per cent on the first day after operation, by the sixteenth day the bile acid content was 1.3 per cent. The percentage of cholic acid, however, remained below 0.1 throughout. The percentage of conjugated bile acids was 0.42 on the sixteenth day. One point should be noted here as regards methods of analysis. The method of Schmidt and Dart for conjugated bile acids would have yielded high false results the first four days and excessively low results thereafter. On the other hand, by the method of Gregory and Pascoe no bile acids at all would have been found.

CASE 13.—This case was one of acute cholecystitis, associated with jaundice, as a result of partial obstruction due to an enlarged pancreas. Cholecystectomy and drainage of the cystic duct were performed. Analysis of the bile on the fifteenth day revealed a concentration of total bile acid of 1.08 per cent (table 2). The cholic acid formed 58 per cent of the total bile acid content.

CASE 14.—G. K., a housewife aged 51, was well for eight years after cholecystectomy. She was admitted to the hospital with a history of three attacks of severe epigastric pain, associated with vomiting, during the previous three months. While she was in the hospital, a severe attack of pain developed, associated with jaundice. The icteric index of the blood rose to 45, while at the same time the amylase content of the blood was found to be 42 units (Elman). At operation the stump of the cystic duct as well as the common bile duct was found to be dilated to 1 inch (2.5 cm.) in diameter. Two small bilirubin pigment stones

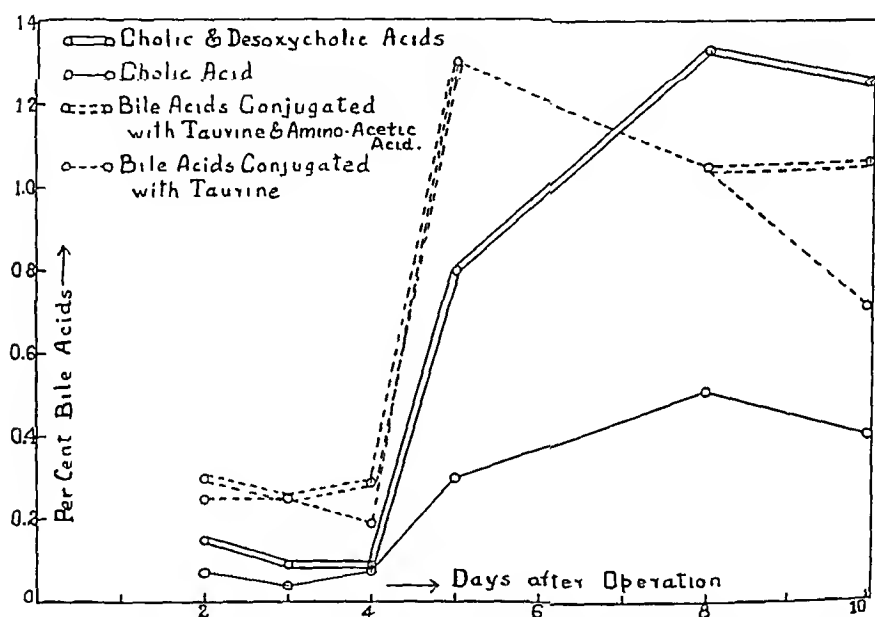


Chart 7 (case 14).—Chart showing the results of bile acid analysis in a case of acute pancreatitis associated with partial biliary obstruction eight years after cholecystectomy. Note the high false results for conjugated bile acids up to the fifth day, the high concentration of bile acids after the fifth day and the presence of the various bile acids in approximately normal proportions on the tenth day. The high concentration of bile acids in hepatic bile noted here was also present in other cases of pancreatitis.

were found in the choledochus. The pancreas was hard and enlarged, producing partial obstruction of the common bile duct. A biopsy specimen of the pancreas obtained with a punch showed acute interstitial pancreatitis and the presence of bile pigment in the fine radicles of the pancreatic duct. Choledochostomy was performed. The patient made a rapid recovery and has been well since.

Analysis of the bile from the fistula (chart 7) showed both the usual low percentage of bile acids during the first four days and also an excessive percentage of conjugated bile acids. On the fifth day, however, the bile acid content had risen to 0.8 per cent, and on the eighth day, to 1.33 per cent. On the tenth

day, the various bile acids were beginning to approach normal proportions; i.e., the cholic acid content was almost half the amount of the total bile acid, while the amount of conjugated bile acid was slightly less than the total bile acid content.

The high percentage of bile acids, in hepatic bile in cases of acute pancreatitis, as noted in cases 13 and 14, was also found in cases 15, 16 and 17 (table 3).

TABLE 3.—*Differential Bile Acid Analysis of Bile from a Fistula in Various Conditions*

Case No.	Days After Operation	Bile Acids Conjugated with		Total Bile Acids Conjugated	Cholic Acid	Desoxycholic Acid	Total Bile Acids	Cholic Acid, Percentage	Free Bile Acid, Percentage	Comment
		Taurine	Ammoniacetic Acid							
15	2	0.26	0.11	0.37	70	..	Pancreatitis; areas of fat necrosis; dilated choledochus; icterus index, 48; bilirubinemia, 3.5 mg.; 12 yr. after cholecystectomy
	5	0.23	0.22	0.52	44	..	
	12	0.23	0.55	0.78	0.77	0.56	1.33	58	42	
16	1	0.22	0.23	0.45	0.12	0.49	0.61	20	26	Acute pancreatitis; gallbladder and choledochus normal; no stones and no jaundice; cholecystostomy
17	1&2	0.50	0.50	0.50	0.10	1.21	1.31	8	62	Acute pancreatitis; chronic cholecystitis with one large stone; dilated choledochus
20	1-6	0.01	0.39	0.43	10	..	Cholangitis; gallbladder and ducts full of precipitated pigment; fibrosis of liver
	7&8	0.05	0.54	0.59	12	..	
21	2	0.006	0.015	0.021	29	..	Cholangitis; partial obstruction with jaundice for 4 mo.; died in cholemia on 6th day after operation
	5	0.016	0.274	0.290	6	..	
22	1	0.009	0.052	0.061	10	..	Carcinoma of papilla of Vater with obstruction; cholangitis and pericholangitic abscesses; died on 3d day
	2	0.009	0.015	0.024	37	..	
24	2	0.20	0.07	0.36	0.19	0.66	0.85	22	57	Chronic cholecystitis; dilated thickened choledochus containing one stone; incomplete obstruction; bilirubinemia, 1.2 mg.; increased number of leukocytes in periportal fields
	6	0.13	0.13	0.26	0.07	0.21	0.28	24	7	
	14	0.09	0.13	0.22	0.09	0.50	0.59	23	44	
	28	0.49	1.08	1.57	0.65	1.21	1.86	35	16	
27	1-3	0.16	0.20	0.36	0.06	0.15	0.21	28	..	Hepatic degeneration and acute cholangiolitis
	8	0.10	0	0.10	0.01	0.03	0.04	25	..	

In case 15 the high proportion of cholic acid on the second day is to be noted. On the twelfth day the concentration of bile acid was 1.33 per cent. In case 16 the concentration of bile acid was 0.61 per cent on the first day of drainage by cholecystostomy for acute pancreatitis. In case 17 the bile drained the first and second day had a concentration of 1.31 per cent. The cholic acid content was only 8 per cent of the total bile acid content.

Group II.—Cases in which infection of the biliary tract was predominant.

CASE 18.—E. S., a woman aged 74, gave a history of attacks of pain in the right upper quadrant of the abdomen of one and one-half years' duration, accompanied by chills. She was jaundiced for three weeks before operation. The icteric index of the blood was 22, and the bilirubin content of the blood was 1 mg. per hundred cubic centimeters. There was incomplete biliary obstruction. At operation the gallbladder was found to be distended and thin walled. The choledochus measured $\frac{1}{2}$ inch (1.27 cm.) in diameter and contained three large bilirubin stones. Choledochostomy was performed. Convalescence was progressing smoothly when pneumonia suddenly occurred on the twelfth day, and the patient died on the eighteenth day. Autopsy revealed bilateral lobular pneumonia of the inferior lobes. A duodenal diverticulum was present. There was marked and widespread cholangitis.

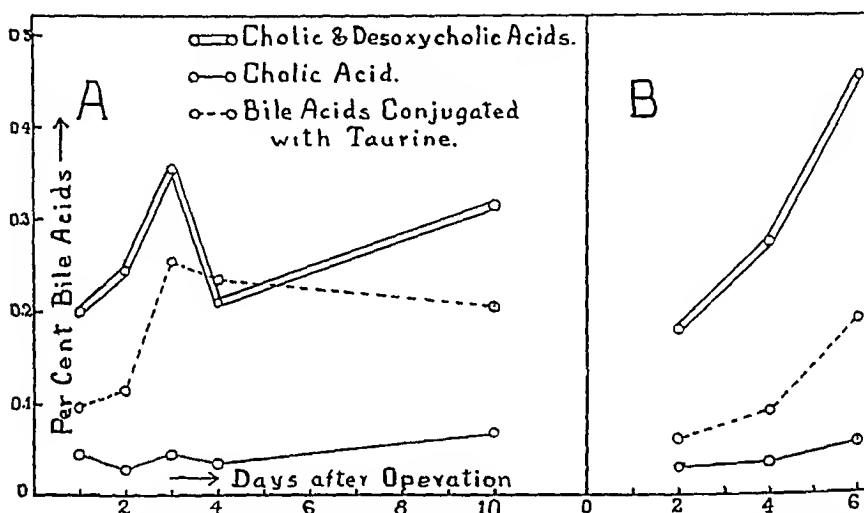


Chart 8 (case 18, 8 A and case 19, 8 B).—Chart showing the results of bile acid analysis in a case of widespread cholangitis. Note the low ratio of cholic acid, the presence only of taurine-conjugated bile acids and the high proportion of free bile acids in B.

The results of the bile acid analysis of the bile from the fistula (chart 8 A) are typical of those in cases of cholangitis. It is to be noted that the proportion of cholic acid to the total bile acids remains consistently low, and that the conjugated bile acids are expressed wholly as taurine bile acids owing to the fact that the aminonitrogen, as calculated from the sulfur present, was found to be as high or higher than the total aminonitrogen, as determined by the gasometric procedure of Van Slyke.

CASE 19 (chart 8 B).—Analysis yielded results similar to those in case 18. Fibrosis of the liver was noted, and a biopsy specimen obtained by means of a punch revealed a marked exudate of polymorphonuclear and lymphocytic cells in the periportal fields. A cyst was found in the choledochus. The drainage of bile from the common duct revealed *Bacilli coli* on culture. Although the total bile acid content rose to 0.45 per cent on the sixth day, only a trace of cholic acid was present throughout. Only taurine-conjugated bile acids were found.

CASES 20, 21 and 22.—These cases are similar examples of cholangitis. In case 20 operation for subacute cholecystitis associated with jaundice revealed the gallbladder and ducts to be full of precipitated pigment. The liver appeared to be fibrosed. The cystic duct was drained. As can be seen in table 3, analysis of the bile revealed a low proportion of cholic acid. In case 21 operation revealed a shrunken gallbladder. A stone impacted in the cystic duct protruded into the choledochus and caused partial obstruction, which had produced slight jaundice for a period of four months. Cholangitis was present. Choledochostomy was performed. The patient died on the sixth day in cholemia. The bile was pale and thin, and, as can be seen in table 3, analysis on the first day revealed only a trace of bile acids. On the sixth day, before death, the bile acid consisted almost wholly of desoxycholic acid.

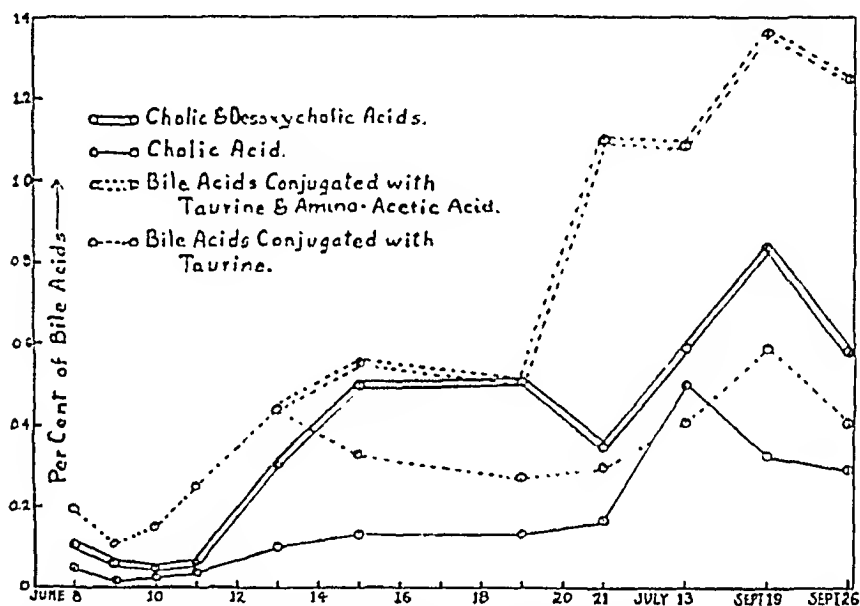


Chart 9 (case 23).—Chart showing the results of bile acid analysis in a case in which choledochostomy was performed for acute cholangitis, which occurred four months after cholecystectomy and removal of a stone from the common bile duct. Note the low cholic acid ratio up to the time when the inflammation in the bile ducts was overcome, the high cholic acid ratio on July 13 after the closure of the tube for several days, and the high false results for the conjugated bile acids persisting after disappearance of the inflammation. These results were associated with the presence of pancreatic enzymes in the bile.

Case 22 (table 3) represents the results of an analysis of bile acids in a 48 year old man who at operation was found to have a carcinoma of the papilla of Vater with complete obstruction. Cholecystostomy was performed. On the first day 870 cc. of dark, concentrated-looking bile was drained, while on the second day 1,770 cc. of bile was collected. The patient died three days after operation. At autopsy acute cholangitis and pericholangitic abscesses were found. The bile, although very dark, was found to have only a trace of bile acids.

CASE 23.—F. J., a housewife aged 49 years, first had attacks of pain in the right upper quadrant of the abdomen in January 1934. In July 1934, jaundice

and pruritus developed, and the stools were clay colored. In October 1934, *choledochostomy and cholecystectomy* were performed. After removal of a stone from the common bile duct she was well for three months, when symptoms of epigastric pain, chills, fever, vomiting, icterus and pruritus recurred. She was admitted to this hospital, and operation was performed on June 8, 1935. The choledochus was found to be dilated and thickened and containing infected bile full of inspissated material. Culture yielded a growth of *B. coli*. Biopsy of the liver showed only slight thickening of the periportal fields. A T-tube was inserted, and drainage was carried out for fourteen weeks. During the latter ten weeks the tube was closed off for sixteen hours every day. It was finally removed, and the fistula closed in two days. The patient remained well for five weeks, when the whole train of the original symptoms recurred. Reoperation was performed on Dec. 4, 1935. Severe cholangitis was again found, and in addition biopsy of the

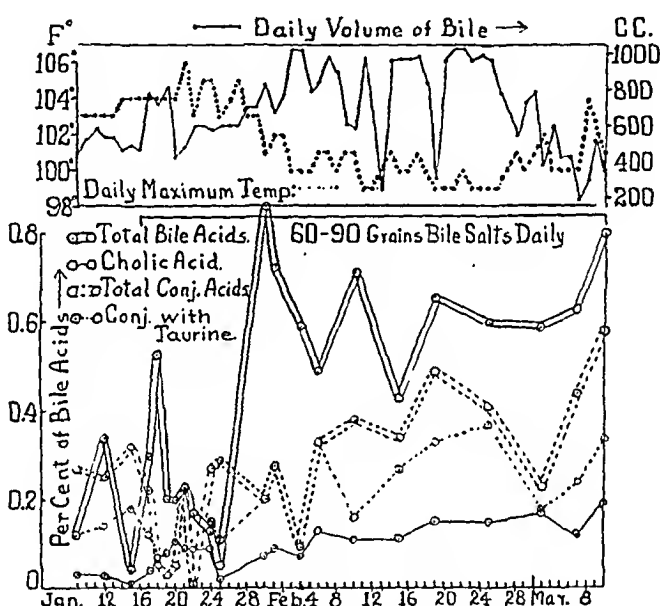


Chart 10 (case 23).—Chart showing a summary of the bile acid analysis starting one month after reoperation for recurrence of cholangitis and cholangiolitis. Note the low concentration of bile acids in association with cholangiolitis (January 9 to 24), the effect of feeding large amounts of bile salts by mouth, the concentration rising from 0.2 to 0.8 per cent and the volume of bile increasing from 600 to 1,000 cc. daily and the persistently low ratio of cholic acid. Note also that as the fever increases the volume of bile falls.

liver showed widespread chronic pericholangiolitis. Since the operation bile has continued to drain, and the patient has slowly been getting worse. Bouts of high fever have recurred. Drainage has been kept up continuously through the tube.

Chart 9 summarizes the bile acid analysis of the bile from the fistula after the first operation. It can be seen that during the first weeks the proportion of cholic acid was typically low in proportion to the total amount of bile acids, as in other cases of cholangitis. The conjugated acids tended to be higher than the total bile acids. Isolated analyses during the next three months, when the patient

was apparently well and the bile was clear, indicated that the cholic acid was in normal proportion. On July 13, however, cholic acid was 85 per cent of the total. This analysis was done shortly after the tube had begun to be clamped off daily. One extraordinary finding can be noted especially. The analyses performed after June 21 showed a high false result for the conjugated bile acids, although the cholic acid ratio was in normal proportion.

After the second operation the bile acid analysis of the drainage material (chart 10) was carefully followed, especially in relation to the temperature curve, the volume output of bile and the effect of oral administration of large amounts of pure bile salts. The bile salts were given both to improve the nutrition of the patient by increasing absorption from the intestinal tract and to increase the excretion of bile in an attempt to flush out the infection. As can be seen from the chart, the bile salt therapy was begun over one month after the second operation. During that period the patient had a consistently high intermittent fever, and the fistula drained daily from 60 to 120 cc. of bile containing a low percentage of bile acids. With the administration of bile salts, the volume output of bile acids rose markedly. But it is to be noted that when the temperature rose the volume of bile tended to diminish, although the percentage of bile acids stayed up. The bile acid analysis shows the consistently low ratio of cholic acid to total bile acids, in spite of the fact that the bile salts given orally contained about 80 per cent of cholic acid. In addition, the excreted bile acids were preponderantly in the form of free bile acids.

CASE 24.—J. J., a salesman aged 44, first had severe attacks of right subcostal pain seven months previous to his admission to this hospital. The attack persisted for three weeks. At the same time he was found to have diabetes. He had four similar attacks afterward, the last one occurring four days before admission. The last two attacks were accompanied by fever, the temperature rising to 101 F., and icterus. On the patient's admission the icteric index was 9, and the bilirubin content of the blood was 1.2 mg. per hundred cubic centimeters. Urobilin was present in the stool. Before operation the icteric index had fallen to 5 and the bilirubin content of the blood was 0.4 mg. At operation the gall-bladder was found to be shrunken and thickened. An old perforation into the bed of the liver was present, where stones were found. The choledochus was markedly thickened and dilated to 1 inch (2.5 cm.) in diameter. A cholesterol stone was found in the retroduodenal portion. Cholecystectomy and choledochostomy were performed. Biopsy of a specimen from the liver revealed a conspicuous number of bile thrombi and an increase in the number of leukocytes in the periportal fields. The choledochostomy T-tube was clamped on the twenty-second day. After six days the tube was opened, a sample of bile was obtained and the tube was removed. Convalescence was uneventful, and the patient has been well since.

This case is added not only to demonstrate the low cholic acid ratio in cases of cholangitis and cholangiolitis, but also to present an analysis of a fairly normal sample of hepatic bile (table 3). Thus when the tube was clamped off for six days the enterohepatic cycle was completely reestablished, and a sample of normal bile could then be obtained by tapping the tube. When the tube was opened for a short period, the sample of bile obtained had bile acid in a concentration of 1.86 per cent, of which 35 per cent was cholic acid. The slightly low cholic acid ratio may have been due to some residual infection in the biliary tract. The indications are that approximately normal hepatic bile contains almost 2 per cent bile acids.

GROUP III.—Cases of acute hepatitis.

CASE 25.—F. R., a 57 year old woman, had a feeling of epigastric distention three weeks before operation. One week later pruritus and marked jaundice occurred. At operation a large, smooth liver and an enlarged spleen were found. The gallbladder and extrahepatic bile ducts were empty of bile and were very edematous. Cholecystostomy was performed. A biopsy specimen of the liver showed acute hepatitis. Small amounts of dark bile drained for a short time. The jaundice decreased rapidly, and the patient was discharged as well.

The bile acid analysis (chart 11) showed a high concentration of free bile acids the first few days and especially a high proportion of cholic acid, apparently characteristic of hepatitis. The rapid fall in the concentration of bile acids was probably due to absorption of the bile acids from the inflamed gallbladder as a result of irritation of the drainage tube.

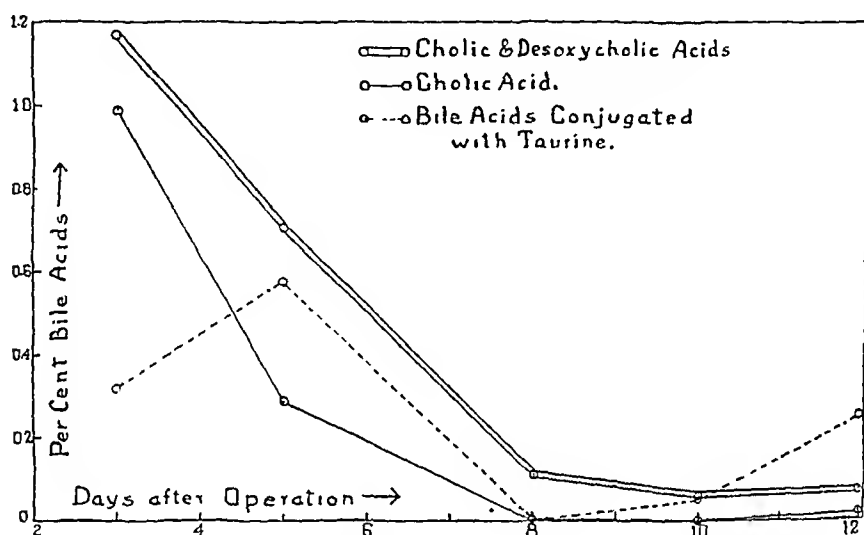


Chart 11 (case 25).—Chart showing the results of bile acid analysis in a case of acute hepatitis in which cholecystostomy was performed. Note the high concentration of bile acids at the onset of drainage and their disappearance after the first day; especially to be noted is the high cholic acid ratio at the onset of drainage and also the presence of taurine-conjugated bile acids only.

CASE 26.—F. W. F., a housewife aged 44, began to suffer from attacks of epigastric pain radiating to the back three years previously. Six months before her admission to the hospital marked weakness and severe pruritus developed. She was admitted to the Mount Sinai Hospital, and a thorough investigation was made. Nothing abnormal was discovered except rather marked anemia and achlorhydria. Two weeks after her discharge mild jaundice developed, which was at first intermittent but more recently increased slowly. The stools became light in color, and the urine very dark. The patient began to lose weight. There was no fever or chills, but chilly sensations were noted occasionally. Pruritus became severe.

The liver was enlarged, smooth and very tender. The spleen was not palpable. The icteric index was 50. At operation the gallbladder was found to be normal,

being neither distended nor dilated. The common duct was not dilated. The liver was large and smooth. A biopsy of the liver showed acute interstitial hepatitis. Choledochostomy was performed.

The results of the bile acid analysis (chart 12) are very similar to those in case 25. The first two days the total percentage of bile acids was quite high but subsequently fell to zero (on the seventh day) and then rose again. The ratio of cholic acid was very high on the second day (81 per cent of the total bile acid content) and then fell to 63 per cent on the third day and 44 per cent on the fifth day. On the tenth day the ratios of the different bile acids were beginning to approach normality.

CASE 27.⁴—S. C., a white man aged 48, was admitted to the Hospital for Joint Diseases with a history that for three weeks he had attacks of pain in the

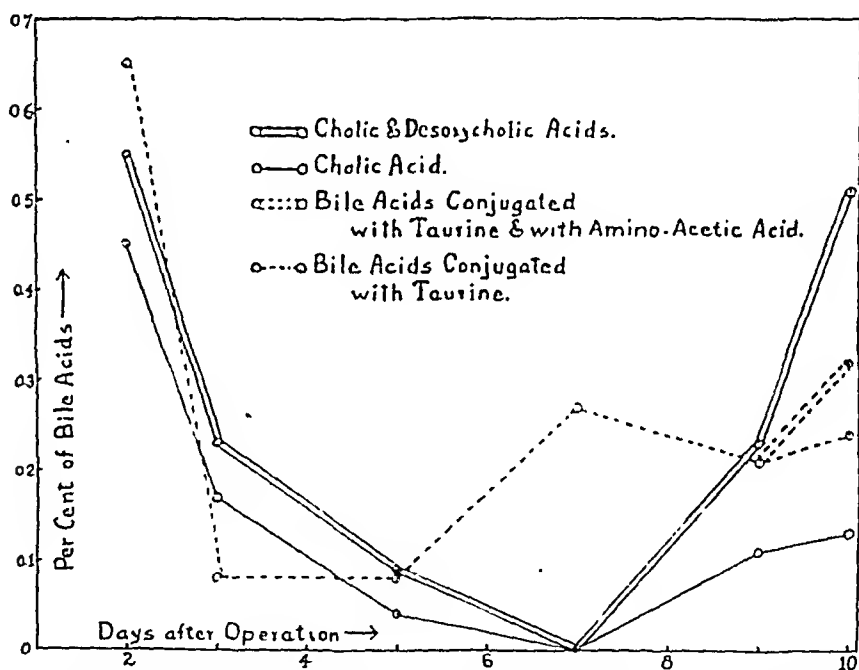


Chart 12 (case 26).—Chart showing the results of bile acid analysis in a case of acute interstitial hepatitis in which choledochostomy was performed. Note the high concentration of bile acids at the onset of drainage, the fall to zero on the seventh day and the rapid rise on the tenth day, the high cholic acid ratio during the first few days of drainage, and the presence of the various bile acids in almost normal proportions by the tenth day.

right upper quadrant radiating to the back, lasting from one to two hours and accompanied by vomiting. There were no chills. The pain became continuous; there were progressive jaundice, clay-colored stools and dark urine. There was a loss in weight of 14 pounds (6.4 Kg.). On his admission to the hospital, however, the patient, although highly icteric, looked well nourished. The liver was enlarged 4 fingerbreadths below the costal margin and was tender to pressure. The spleen could not be palpated. The icteric index of the blood

4. Presented by permission of Dr. A. J. Beller and Dr. H. L. Jaffe.

was 120. At operation bile-stained fluid was found in the peritoneal cavity. Acute cholecystitis and hepatitis were present. The gallbladder and common duct were not distended and contained no bile. Choledochostomy was performed. A biopsy specimen of the liver revealed the presence of both widespread degeneration of the liver cells and severe cholangitis and pericholangitis. After a stormy course, the patient was discharged well.

Analysis of several specimens of bile obtained by drainage revealed a low percentage of total bile acids, of which the cholic acid formed 25 per cent.

COMMENT

At the onset, one should emphasize that all the laboratory findings should be interpreted with great caution because they are based on material in which several varying factors may be present in any one case. Our concept of the proportions of the different bile acids in normal bile is based on scanty material and on bile from fistulas, which fundamentally must be considered abnormal. It is for these reasons that such a large series of cases is presented and that the history of most of them is given in some detail.

Frequent references are made throughout this presentation to other methods of analysis as compared with the results given here. This is done to emphasize the point that any single method of analysis is often open to large errors. The interpretation of such results as reported in the literature must be accepted with great caution.

In a previous report it was shown that in many cases of acute cholecystitis, analysis of the bile by the method of Schmidt and Dart gave results which were much higher than the amount of bile acids actually present. These excessively high and false results were undoubtedly due to the presence of an alcohol-soluble aminonitrogen-containing material which was not derived from the bile acids. The most probable source of this material was the inflammatory exudate. In most of the cases presented here it can be seen that both after the release of obstruction and in the presence of inflammation of the bile ducts the same type of result is found. During the first few days the conjugated bile acids, as estimated by the hydrolyzable aminonitrogen, are frequently found to be much higher than the total bile acids actually present. It would seem that in the bile from a fistula also the presence of any inflammatory exudate would best explain the false results obtained by the method of Schmidt and Dart.

In addition it is to be noted that in these cases the conjugated bile acids appear as mostly conjugated with taurine. This result is undoubtedly due to the presence in pathologic bile of alcohol-soluble sulfur compounds which are included in the sulfur determination used to estimate the taurine. As a result, the excessively high figures for sulfur mask the presence of any bile acids conjugated with amino-acetic acid which may be present.

In several instances, notably in cases 7 and 23 (charts 4 and 9), excessively high figures for conjugated bile acids were obtained after prolonged drainage. In both of these cases, pancreatic enzymes, apparently due to reflux of pancreatic juice, were found in the bile. The high figures for conjugated bile acids could then be explained as due to the splitting of protein into alcohol-soluble aminonitrogen-yielding material. Similar results are obtained on analyzing bile drained from the duodenum. Even if analyzed immediately, such material will yield higher results for the conjugated bile acids than for the total bile acids. In addition, the longer the material is allowed to stand the higher will be the figures for the conjugated bile acids. Thus, a sample of duodenal bile was divided into portions. One portion was analyzed immediately, while the other was allowed to stand for twenty-four hours at room temperature. The results were as follows:

	Immediate Analysis, Per Cent	After 24 Hours, Per Cent
Bile acids conjugated with taurine	0.16	0.16
Bile acids conjugated with amino-acetic acid	0.53	0.90
Total conjugated bile acids	0.68	1.06
Cholic acid	0.16	0.16
Desoxycholic acid	0.31	0.32
Total bile acids	0.47	0.48

It is to be noted that although the results of the analysis of sulfur, which were used to calculate the taurine-conjugated bile acids, remained unchanged, the percentage of total conjugated bile acids rose markedly. The amounts of cholic and desoxycholic acids were found to be unchanged after twenty-four hours. The only explanation for these changes must be that the pancreatic enzymes hydrolyzed a portion of the protein present, and so formed alcohol-soluble nitrogenous material.

It is difficult to account for the sudden drop both in the volume of bile and in the percentage of bile acids that occurs in most cases between the third and the fifth day. Two explanations are possible. One is that the inflammatory reaction of the choledochus after operative trauma results in the absorption of a part of the bile acids. The other and more likely explanation is that after the release of obstruction the bile acids present in the fine bile ducts throughout the liver are washed out during the first two or three days. The liver itself, as a result both of the obstruction and of the operative trauma, begins to manufacture bile acids only after several days. The concentration of bile acids in the hepatic bile then increases gradually. Cases 1 and 2 are good examples of the gradual functional recovery of the liver.

It is a difficult matter to form some estimate as to the proportions of the various bile acids in normal bile. It is evident that after a few

days of drainage (as in cases 1, 2, 3, 4, 5, 8, 13, 14 and 15) the various bile acids tend to be present in definite proportions. The cholic and desoxycholic acids tend to be in equal proportions, and the percentage of taurine-conjugated bile acids is about one-half the total conjugated bile acid content, which in turn form about 80 per cent of the total bile acid content. In a previous report on the bile acid composition of bile from the gallbladder, somewhat similar findings were noted in cases in which the gallbladder was normal.

On analyzing the results of the whole series of cases, the variations in the ratio of cholic acid to desoxycholic acid seem to be the most important findings (chart 13). Essentially it can be seen that

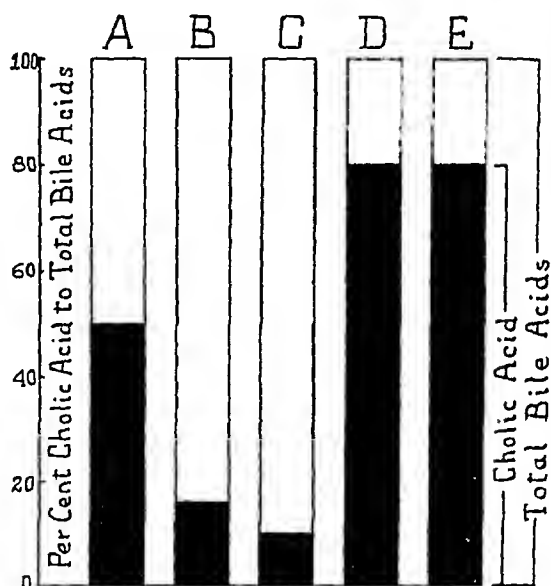


Chart 13.—Summary of findings of the ratio of cholic acid to total bile acids in the bile drained through a fistula in various conditions. In *A*, the cholic acid forms approximately one half of the total bile acid content in apparently normal bile; in *B*, widespread cholangitis, only about one sixth of the total bile acid content is found to be cholic acid; in *C*, long-standing intermittent biliary obstruction, only about one tenth of the total bile acid content is cholic acid; in *D*, acute obstruction, cholic acid forms about four fifths of the total bile acid content, and in *E*, acute hepatitis, about four fifths of the total bile acid content is cholic acid.

after the release of noninflammatory obstruction the percentage of cholic acid to the total bile acid content appears to be about 50. Cases 1, 2, 3, 4, 5, 8, 13, 14 and 15 are examples. In cases in which inflammation of the bile ducts is the predominating factor the cholic acid invariably forms a very low percentage of the total bile acids. Cases 18 and 19 (chart 8), cases 20, 21 and 22 (table 3) and case 23,

after the first operation (chart 9) until the infection cleared up, and throughout the period after the second operation (chart 10), are all examples of such conditions. In cases in which hepatitis was the predominating pathologic condition the cholic acid tended to form a high proportion of the total bile acids. Cases 25 and 26 (charts 11 and 12) are good examples illustrating the results of analysis of such conditions. The extraordinarily high percentage of bile acids after drainage during the first three or four days in such conditions is a noteworthy finding. It seems most likely that this large concentration of bile acids must be due to the washing out of the bile passages as a result of drainage. In case 26 (chart 12) the bile acids were in the normal proportions by the tenth day. It is evident that in this case the operative procedure in a case of acute hepatitis not only had done no harm but actually seemed to have hastened the onset of recovery. As a matter of fact, in all three cases of hepatitis presented here the operative procedure was apparently beneficial. French observers have reported similar good results.⁵

Certain exceptions to the foregoing findings must be made. In case 7 (chart 4) both obstruction due to stone and cholangitis were present. It can be noted that the ratio of cholic acid was low throughout, typically that seen in cholangitis. In case 6 (chart 3) and in case 12 (chart 6) the most notable feature is the extraordinary high percentage of free desoxycholic acid. In both cases there was a history of long-continued intermittent obstruction. In case 6, as a result of obstruction by stone, and in case 12, as a result of stricture, these findings of the very low percentage of cholic acid and of the very high percentage of free desoxycholic acid may be due to injury to the liver cells as a result of the long-continued intermittent obstruction. In a number of cases in which there was sudden acute obstruction without infection an opposite condition was present. Cases 9, 10 and 11 (table 2) are examples. Here the percentage of cholic acid tended to be high, sometimes 70, 80 or 100 per cent of the total. In all these cases there was sudden acute obstruction associated with jaundice. The gallbladder in these cases was absent or shrunk and fibrosed, so that its action as a safety valve was absent. As a result, in sudden acute obstruction the brunt of the back pressure would be borne by the liver cells themselves. Case 23 (chart 9, July 13) is an example of the results of an acute obstruction. In this case there had been long-continued drainage through a T-tube for one month. On July 10 the patient had begun to tie up the tube for a period of sixteen hours each day. Analysis of the bile on July 13 showed that the cholic acid

5. Chabrol, E.; Brocq, P., and Porin, J.: *Les enseignements de la cholécystotomie dans les ictères infectieux*, Presse méd. 40:1053 (July 6) 1932.

instead of being 50 per cent of the total bile acid content had risen to 83 per cent of the total. This sudden rise was apparently due to acute obstruction after the closure of the tube in a case in which the sphincter of the common duct was spastic. That acute injury to the liver cells may be the cause of a high cholic acid ratio is supported by the evidence found in cases of acute hepatitis (cases 25 and 26). In these cases it was evident on histologic examination that there was widespread injury to the liver cells, and here also the cholic acid ratio was very high.

In cases in which there was associated pancreatitis (case 13, table 2; case 14, chart 7; cases 15, 16 and 17, table 3), one outstanding point is to be noted, viz., the percentage of bile acid tended to be very high. In case 13 the bile contained 1.08 per cent of bile acids on the fifteenth day. In case 14 (chart 7) the bile contained 1.35 per cent of bile acids on the eighth day. Similar high percentages of bile acids were found in cases 15, 16 and 17 (table 3). These findings are of great interest in the relation to the point of view held by many investigators that acute pancreatitis is often due to regurgitation of bile into the pancreatic duct. That this theory is correct is supported by our finding in case 14 of bile-filled ducts in a biopsy specimen of pancreas removed at operation. It is evident that if a reflux of bile causes pancreatitis, such an event can occur only if the bile contains a high percentage of bile acids, since it was shown long ago by Flexner⁶ that the important toxic element in bile is the bile acids. The finding of a high concentration of bile acid in the hepatic bile in all our cases of pancreatitis is strong evidence in support of the view that in many cases pancreatitis is produced by the reflux of bile into the pancreatic ducts.

The analyses in case 27 form a good example of the results produced when a combination of two factors is present. In cases of cholangitis the cholic acid forms about 15 per cent of the total bile acid content. In cases of hepatitis cholic acid forms about 80 per cent of the total bile acid content. In case 27 both conditions were present at the same time, and the cholic acid was found to be 28 and 25 per cent of the total bile acid content.

The low cholic acid ratio found in all cases of inflammation of the bile ducts requires close consideration. In a previous paper it was shown that in cases of acute cholecystitis with obstruction of the cystic duct the bile acids were absorbed in a differential manner. The more prolonged the obstruction, the lower the cholic acid ratio fell, indicating that the cholic acid was absorbed much more readily than the desoxycholic acid. Since in cases of acute cholangiolitis the bile flows

6. Flexner, S.: The Constituent of the Bile Causing Pancreatitis and the Effect of Colloids upon Its Action, *J. Exper. Med.* 8:167 (Jan.) 1906.

through innumerable fine bile canaliculi, there is a strong possibility that the bile acids are absorbed by the inflamed walls of the ducts. The finding of a low cholic acid ratio in a case of acute cholangitis supports this theory. Chart 10 (case 23) presents a summary of a typical case of widespread cholangiolitis followed in great detail. As can be noted, the volume of bile decreases as the temperature rises and increases as the temperature falls, indicating that during the more acute phases of inflammation more bile was absorbed. Even the bile that was excreted contained only a low percentage of bile acids. The same is found in other cases of cholangitis (cases 20, 21 and 22). When bile acids were fed in large amounts (from 60 to 90 grains daily [3.9 to 5.8 Gm.]) the cholic acid ratio remained persistently low despite the fact that the bile acids administered contained 80 per cent of cholic acid. It is evident that the bile acids were absorbed from the intestine and excreted by the liver, but during their passage down the bile ducts it appears that the cholic acid was absorbed much more readily than the desoxycholic acid, which was excreted partly as free and partly as conjugated acid. Another point indicating that bile was absorbed from the inflamed bile ducts was the appearance of bile pigment in the urine every time the temperature rose and the volume of bile decreased. This occurred in spite of the fact that there was no obstruction and bile was being excreted in large quantities. It would seem, therefore, that in cholangiolitis both bile salts and the bile pigment are absorbed by the inflamed walls of the bile ducts.

CONCLUSIONS

1. After the release of obstruction uncomplicated by infection the cholic acid of hepatic bile forms about 50 per cent of the total bile acid content.
2. In the presence of inflammation of the bile ducts, cholic acid forms about one sixth of the total bile acid content. This low cholic acid ratio indicates that the bile acids are probably absorbed by the inflamed bile ducts.
3. In cases of acute obstruction of the biliary tract in which the gallbladder is absent cholic acid forms about four fifths of the total bile acid content.
4. In cases of acute hepatitis cholic acid forms about four fifths of the total bile acid content.
5. In all cases of pancreatitis presented here, the hepatic bile was found to contain a high percentage of bile acids.

A REVIEW OF UROLOGIC SURGERY

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(Concluded from page 1116)

TRANSURETHRAL SURGERY

Thompson,³⁶ in a report concerning transurethral operations performed at the Mayo Clinic during 1935, called attention to the use of sodium ethyl-1-methylbutylthiobarbituric acid in producing anesthesia. This drug is injected intravenously and seems unusually well suited to urologic practice. This anesthetic is suitable for cystoscopic examinations, manipulation of ureteral stones, removal of vesical tumors, litholapaxy and transurethral prostatic resection, in fact for almost any type of transurethral procedure which can be completed within thirty minutes.

During the year 63 patients with neoplasm of the bladder were treated by transurethral methods, involving destruction by electrocoagulation or excision of the growth with either an operating cystoscope or the Stern-McCarthy resectoscope. Until a few years ago the

36. Thompson, G. J.: Transurethral Surgery in 1935, Proc. Staff Meet., Mayo Clin. 11:360-363 (June 3) 1936.

transurethral destruction of all but very small vesical neoplasms involved repeated cystoscopic treatments which often extended over a period of several weeks or months. At present practically any pedunculated growth can be removed in one sitting. Those tumors which infiltrate the wall of the bladder should, of course, be removed suprapubically. However, in a number of cases of this type the general condition of the patient precluded major operation, and therefore radon emanation seeds were implanted through the cystoscope.

Thirty-three patients were subjected to 39 operations in an attempt to remove calculi from the ureter. In 25 of these cases the stone was removed at the time of manipulation, in most instances with the Councill stone extractor. This instrument must be used carefully, or severe injury to the ureter and a serious postoperative reaction will ensue. In 5 additional cases the stone was passed a few days or a week after manipulation with little discomfort to the patient. The transurethral method was therefore successful in more than 90 per cent of the cases.

There were 695 patients who had urinary obstruction due to benign or malignant involvement of the prostate gland on whom a total of 765 prostatic resections were performed. Attention is called to the fact that 35.4 per cent of these patients were more than 70 years of age, and only 7 per cent were less than 55 years of age. These figures are contrasted with those for a group of 1,922 patients who were accorded prostatectomy prior to 1932, of whom 20.4 per cent were more than 70 years old, indicating that a considerable number of elderly men who formerly refused or were denied prostatectomy are presenting themselves and are being referred for transurethral resection. Thompson expressed the belief that transurethral resection can be done safely at any time when the volume output of urine is more than 1,500 cc. daily and the patient is free from fever. No attempt was made during the year to reduce the degree of pyuria to a minimum prior to operation. It was felt that the urinary infection could be more easily dealt with after the patient was able to empty the bladder by normal urination. This change in attitude concerning the necessity of preoperative preparation has resulted in a still shorter stay in the hospital and consequently less expense for the patient. The average postoperative stay in the hospital for the entire group was eight and three-tenths days.

There was no mortality from any of the transurethral procedures (a total of 2,851 procedures on 1,521 patients) except in the group of patients undergoing prostatic resection. Of the 695 patients who were subjected to transurethral resection, 7 died, a mortality of approximately 1 per cent.

PROSTATE GLANDS

Prostatitis.—Grant³⁷ in 1933 stated that the etiology of prostatitis is due to the gonococcus in from 75 to 90 per cent of cases. Whatever the original cause, in a very short time the cultures of the expressed prostatic secretion reveal mainly growths of *Staphylococcus albus* and *Bacillus coli*. The termination of acute prostatitis is resolution or the development of abscess, or chronic prostatitis. The structure of the prostate gland, with its multitude of ramifications of acini, gives deep-seated pockets to the invading organisms, the path of approach of which in most cases undoubtedly is along the mucus-lined passages from the posterior portion of the urethra. Almost all methods of treatment are bent toward the reverse of this march by promoting the flow of infected material outward into the urethra again. Treatment by diathermy tends to increase the flow from the infected pockets by heating the gland and by improvement of the circulation. Massage is done for the purpose of pushing the infection out and somewhat as a stimulation to the circulation. Grant stated that, considering the pathologic anatomy, little can be accomplished by massage except to empty a few overdistended acini, and many must be pressed in more tightly. The incidence of epididymitis following massage is too frequent to recall with pleasure.

The treatment of prostatitis from a systemic base has been advocated by many proponents of treatment with foreign serums. Young, Colston and Hill have treated some patients by the intravenous injection of a solution of mercurochrome. Grant stated that it seems impossible to apply any medication to the interior of the prostate gland through the urethra. Lavage of the urethra can only affect the mouths of the prostatic ducts and can accomplish little as a cure. He recalled that Townsend, in 1917, in collaboration with Valentine and Cano, suggested a method of treating the gland by intraprostatic injections of solution of methylphenol and a normal phenol serum. Grant concluded that since mercurochrome was nontoxic and nonirritating a good plan would be to inject the solution into the interior of the gland with the reasonable assurance that the antiseptic would then come in direct contact with the infectious organisms. His technic is to fill the bladder with water and then introduce a 6 inch (15.24 cm.) 22 gage needle through the perineum into the prostate gland, guiding the needle with a finger in the rectum. From 10 to 20 cc. of solution of mercurochrome is injected at various points throughout the gland, and gentle massage follows to disseminate the drug. Grant stated that there is little pain from the injection. The patients complain of a sense of distention in the prostatic region, which is immediately relieved by voiding. He stated

37. Grant, Owsley: Treatment of Prostatitis by Injection, *J. Urol.* 29:749-753 (June) 1933.

that the first hundred patients were selected because they had chronic prostatitis without evidence of disease of the vesicles. Since then he frequently accompanies the procedure of intraprostatic injection with vasopuncture and injections of mercurochrome through the vas. He stated that 400 patients have been so treated without a single untoward result. Grant is of the opinion that the end-results he obtains by this method are most satisfactory.

Grant,³⁸ in 1935, stated that the early steps in the treatment of chronic prostatitis by injection should be taken with exquisite care. First he "injected a few dogs' glands and they seemed none the worse"; then he hospitalized 25 patients for a week after injection, and no untoward symptoms developed; then he had 50 ambulatory patients make a report daily. The latter had no distress. He stated that in 500 cases he never had any cause to question the complete safety of the procedure. In some cases the drug was undoubtedly partially injected outside the capsule without any deleterious effect. Patients with chronic prostatitis received the most benefit. No conclusive data have been available for study of resultant pathologic changes. No sexual disturbance was complained of. At the time of perineal injection into the prostate gland, both vasa are injected with 10 cc. of a 1 per cent aqueous solution of mercurochrome. The average injection directly into the prostate is 20 cc. (10 cc. into each lateral lobe) of a 1 per cent solution of mercurochrome. After injection the gland is massaged by rectum to disseminate the fluid through the gland. The urethral method of injection is accomplished with a specially constructed needle through a McCarthy panendoscope under direct vision. The follow-up treatment consists of heat applied to the gland and massage every fifth day. The usual course of the latter lasts about from three to five weeks after operation, until all pus has disappeared and culture of the expressed secretion is sterile.

Grant stated that he does not attempt to say definitely how mercurochrome injected into the prostate gland acts. It is his belief "that in this type of injection the mercurochrome acts with definite germicidal properties, and since it does remain in the gland and vesicles for an extended period (prostatic secretion often tinged for as late as four weeks) it prevents further bacterial growth. It does not seem likely that it acts in some obscure biological way as it does when injected intravenously. Indeed, the entire basis of our hypothesis is the introduction of some antiseptic directly into the seat of inflammation in an endeavor to check that process by direct action."

38. Grant, Owsley: The Treatment of Chronic Prostatitis by Injection, J. Urol. **33**:631-638 (June) 1935.

McCarthy³⁹ recommended direct intraprostatic injection of from 3 to 8 cc. of medium into each lateral lobe through the panendoscope. The injection is made into the median lobe one week later. In his patients so treated the number of injections varied from three to seventeen.

Cano,⁴⁰ of San Salvador, introduced perineal intraprostatic injection (along with Townsend and Valentine) in 1917. Von Lackum later suggested injection through the anterior wall of the rectum. McCarthy has given injections to 40 patients, of whom all but 2 reported definite improvement. In 16 all symptoms disappeared, and they were discharged as clinically cured.

Townsend⁴¹ stated that in noncooperative patients he has accidentally injected fluids into the prostatic sheath, into the submucous group of glands and even through the membranous urethra into the bladder. The only aftermath was temporary retention of urine due to elevation and blocking of the neck of the bladder and to an increased volume of these submucous groups of glands. Townsend, immediately prior to enucleation, injected alum carmine, methylene blue and india ink into obstructing adenomatous prostate glands. All dyes except the india ink disappeared during the hardening and staining of the specimens. India ink, however, was found distributed irregularly in the prostatic tissue, some pigmented granules within the lumens of the glands as well as in the epithelium, some within blood vessels, involving all the coats, and the remainder diffusely scattered. The body of a criminal, aged 22, was chosen for intraprostatic injection five minutes after his electrocution; 15 cc. of a 20 per cent suspension of india ink in a saline solution was injected into each lateral lobe, and immediately the tissue was removed for section. Under microscopic section the black pigment was diffused in all muscular, glandular and vascular tissue. The epithelial lining of the tubules and alveoli were all more or less extensively stained, partly diffusely and partly in the form of dark pigment granules. Many of the lumens of the glandular structures contained the pigment, as did the walls of the blood vessels and their endothelium. All operators advise placement of injected substances in depots in the gland. Townsend concluded that perineal puncture is the shortest surgical route for attack on the prostate infections, that substances injected into the prostate diffuse throughout the

39. McCarthy, J. F.: *Recent Advances in Instrumental Urology*, J. Urol. **33**: 303-309 (March) 1935.

40. Cano, F. G.; Townsend, T. M., and Valentine, J. J.: *The Intravenous and Intraprostatic Injections of Methyl-Phenol and Normal Phenol Serum in Gonorrhea*, M. Rec. **91**:715-719 (April 28) 1917.

41. Townsend, T. M.: *Intraprostatic Injections*, J. Urol. **35**:75-79 (Jan.) 1936.

gland and that since substances so injected find their way into prostatic blood vessels, no medicament should be introduced into the gland which will not be tolerated by the general circulation.

Toxic Hyperplasia.—Barnes⁴² reported on experiments on animals which were performed to determine if sterile secretion from the prostate gland was toxic and, if so, its effect on animals in comparison with other substances of known toxicity. Mice were given intraperitoneal injections of varying amounts of secretion from this gland. Most of that used contained less than 5 pus cells per high dry field and was obtained by massage of the gland under aseptic conditions; it was proved sterile by cultures before injection. Other specimens were obtained in the ordinary manner without the use of aseptic technic. It was found that there was no difference in the toxic effect between the sterile and the unsterile secretion from the prostate gland, whether originally sterile and containing pus or whether contaminated after being obtained. This is not unusual when the natural immunity of mice and rats to organisms which are pathogenic to human beings is considered.

Secretion from the prostate gland which contained no pus was toxic when injected into mice, rats and other animals, the toxicity of 1 cc. being comparable to that of $\frac{1}{4}$ grain (0.016 Gm.) of morphine. It is the belief of Barnes that an excessive amount of secretion retained in the prostate gland results in absorption of this toxic substance, with resulting general and local toxic symptoms. The term toxic hyperplasia of the prostate gland is used to designate this condition.

Massage or Resection.—Emmett⁴³ reviewed the borderline type of case in which the question arises as to whether urinary symptoms of obstruction are caused by true prostatic hypertrophy or merely by prostatitis or chronic, granular, cicatricial prostatic urethritis. Clearcut cases of any kind are readily recognized by the experienced urologist. Unfortunately, however, all patients do not present signs which make for a definite and unequivocal diagnosis. This group includes the cases in which there are indefinite bars, contractures of the neck of the bladder, slight lobar hypertrophy or chronic cicatricial urethritis. Clinical symptoms are often misleading and of little help. A number of cases of this type have been encountered, and the author adopts the attitude of "when in doubt, give conservative treatment a trial first." This consists of: vigorous prostatic massage, after which the bladder is lavaged with a solution of potassium permanganate (1:8,000). Two or three treatments are given each week for a period of from two weeks to a month

42. Barnes, R. W.: Toxic Hyperplasia of the Prostate Gland, *J. Urol.* **35**:70-74 (Jan.) 1936.

43. Emmett, J. L.: Prostatic Massage or Resection? *Minnesota Med.* **19**:160-165 (March) 1936.

or more. If the prostatic urethra is very cicatricial, the urethra is dilated once or twice. If associated chronic pyelonephritis is present, it is also treated. If the symptoms of urinary obstruction do not improve and if the amount of residual urine does not definitely decrease during this interval of treatment, the inflammatory element is considered of secondary importance to the obstructive factor, and transurethral resection of the neck of the bladder is then performed. The amount of tissue removed under such circumstances is usually small and ranges from 1 to 3 Gm.

After such a procedure the patient almost always empties his bladder completely, and the symptoms are controlled adequately. After a month or six weeks, prostatic massage may be instituted again if any symptoms persist, but this is not usually necessary.

Emmett reported in detail twelve such borderline cases coming under his observation in 1934 in which a preliminary course of conservative treatment failed to give adequate relief, and transurethral resection was necessary. Recently, all 12 patients responded to questionnaires and 8 were completely satisfied with the results. Two patients still complained, some of nocturia, and 2 still had some symptoms of urinary obstruction. Emmett has found the Braasch-Bumpus instrument satisfactory for resecting the neck of the bladder in such cases.

Stone.—Walters and Thiessen⁴⁴ reported 4 cases in which perineal prostatectomy was performed for stone. They concluded that the surgical treatment for prostatic calculus is indicated: first, when the stone is large enough to obstruct the flow of urine; second, when by its size and position it prevents removal by transurethral methods, and, third, when removal of the calculus will allow more adequate treatment of the prostatic and urinary infection. It is obvious from the study of these cases that surgical operation is only a stage in the treatment and that postoperative care is essential to produce amelioration of symptoms or cure.

Carcinoma.—Barringer⁴⁵ stated that examination of small carcinomas of the prostate gland found at necropsy, clinically undiagnosed and undiagnosable, indicated that in about 75 per cent of all cases the posterior lobe of the gland is the site of origin of the growth. When the carcinoma has become sufficiently large to be diagnosed clinically, in most cases it has extended beyond the posterior lobe into the lateral or median lobes and into the sheath of the prostate.

44. Walters, Waltman, and Thiessen, N. W.: Perineal Prostatectomy for Stone: Report of Four Cases, *Minnesota Med.* **19**:177-179 (March) 1936.

45. Barringer, B. S.: The Treatment of Prostatic Carcinoma, *Surg., Gynec. & Obst.* **62**:410-412 (Feb. 15) 1936.

The control of carcinoma of the prostate gland depends on diagnosis in its early stage. Biopsy of tissue secured through the perineum by aspiration has been a valuable aid in determining the severity of the lesion. Tissue from the gland is obtained in about 80 per cent of the cases in which aspiration is carried out, and its pathologic diagnosis depends on special training on the part of the pathologist. The normal prostate gland is shaped like a somewhat flattened cone with its base at the end of the bladder and its apex downward along the urethra. The entire gland is below the bladder. The posterior lobe, because of its location $\frac{1}{2}$ inch (1.27 cm.) below the neck of the bladder, is difficult to irradiate properly by the implantation of radon seeds through the bladder opened suprapubically.

Progress in the operative control of carcinoma of the prostate gland has been slow. The field of operation is small, and surgical removal presupposes much trauma of the carcinomatous tissue. The combination of high voltage roentgen therapy and intraprostatic irradiation affords the only means to control the lesion in these difficult cases. These two methods of treatment should be carried out simultaneously as far as possible. The treatment of retention is by means of transurethral or suprapubic partial prostatectomy with the high frequency loop. This operation is followed by irradiation in accordance with the technic outlined. Modifications of the operation and the dosage of irradiation must depend on the conditions found in the patient treated. A study of 351 consecutive cases of carcinoma of the prostate illustrates what even inadequate irradiation of the gland alone can accomplish. In more than half of the cases in which the disease was controlled were the lesions classified as extensive; that is, the growth had extended beyond the prostatic sheath and involved the base of the bladder or the perivesical lymph nodes. The majority of patients who die usually succumb within the first two years. Twenty-nine (8.3 per cent) were well for three years and 20 (5.7 per cent) for five years. If the carcinoma is considered as controlled, the patient must reveal no signs of carcinoma in the prostate by palpation, by cystoscopy or by biopsy of tissue secured by aspiration. This is also true of the skeletal and other parts of the body which might be affected by the carcinoma. The fact that the roentgenogram revealed metastasis in 156 cases and that in 44 of these (28 per cent) there was metastasis to bone indicated how serious is the problem of control.

Jacobs⁴⁶ stated that within the three years since he has adopted the method of transurethral resection he has performed this operation on 15 of 19 patients who definitely had a malignant growth of the gland.

46. Jacobs, Arthur: Transurethral Resection of the Malignant Prostate with a Review of Fifteen Cases, *Brit. J. Urol.* 7:321-329 (Dec) 1935.

The McCarthy resectoscope was used in all the cases, and the technic was identical with that employed in cases of benign hypertrophy. Pre-operative drainage, either by the indwelling urethral catheter or by the suprapubic route, is the rule, the choice of method depending principally on the degree of renal impairment. Bleeding that results from resection of the malignant prostate gland is usually less than that encountered after the resection of the benign type.

Of the 14 patients who survived operation, 12 were successfully relieved of obstructive symptoms. Of the other 2, 1 required the insertion of a suprapubic tube in spite of the resection, and the other had suprapubic leakage from a previous cystostomy wound even after resection had been performed twice. Jacobs compared the duration of life of these patients with that of 4 other patients with carcinoma of the prostate gland who were treated by different methods within this same period. Three of these underwent suprapubic cystostomy only; 1 lived seventeen months, another five months and the third fifteen days. The fourth patient, who did not have marked obstruction, was treated by means of radium inserted into the prostate gland through a perineal exposure; he survived for one year.

Player⁴⁷ stated that cases of carcinoma of the prostate gland may be divided into two groups, according to the physical findings. In group 1 are the cases of carcinoma in the early stage within the capsule of the prostate, with areas of marked induration and fixation of the gland. In group 2 are the cases in which the growth is in the late stage, with infiltration of the contiguous structures, with or without metastasis and urinary symptoms. In group 1 the stony hardness and fixation can be palpated rectally, and evidence of the fixed gland may be seen on cysto-urethroscopic examination. When there is infiltration of the prostate and the adjoining structures, little, if any, dilatation is observed when the posterior portion of the urethra is filled with water. Radical surgical operation is the method of choice for treatment in group 1, as it offers the only opportunity of permanent cure. Roentgen therapy should precede operation in order to block the radiosensitive cells of the diseased prostate and the nodes into which the lymphatics of the prostate drain.

In group 2, or in cases in which there are no urinary symptoms and in which the roentgen picture is normal, in which there is infiltration of the immediate contiguous structures, the treatment should be the same as that in group 1, with the addition of radium implants, seeds or needles; these are inserted into the infiltrated areas in which excision is contraindicated or impossible. In cases in which metastasis and

47. Player, L. P.: Carcinoma of the Prostate: Treatment, California & West. Med. 44:299-300 (April) 1936.

urinary obstruction have occurred, treatment may be by the following methods: partial perineal prostatectomy, with implantation of radium into the remaining portion of the gland; perineal exposure of the prostate, with the implantation of radium under direct vision into the gland and invaded contiguous structures; suprapubic exposures of the prostate through a cystotomy opening and partial removal of the gland and implantation of radium according to the Ferguson technic; transurethral resection of the obstruction, combined with suprapubic cystotomy and implantation of radium; transurethral resection of the obstruction and high voltage irradiation. The deciding factor in the selection of any method for treatment in the cases in group 2 is usually the condition of the patient, and some patients may even need implantation of the ureters into the bowel, or to the skin when infiltration has extended into the bladder.

Hale⁴⁸ stated that symptoms of carcinoma of the prostate gland are as obscure as those of carcinoma in general. Frequency of urination is the most common symptom. When there is no associated hypertrophy of the gland and the bladder seems to be completely emptied, there often are noted irritation of the deep portion of the urethra and pain in the penis during micturition. Pain, usually the dull aching or rheumatic type referable to the sacro-iliac region, penis, perineum, thighs, inguinal region or suprapubic region, is often an early symptom. Gradual diminution of strength and loss of weight, associated with the other threads of evidence pointing to carcinoma of the gland, are significant but do not occur early.

Early symptoms of carcinoma of the prostate gland may be summarized as follows: Those associated with hypertrophy are frequency of urination, difficulty in urination, urgency and pain in the penis during urination. Those associated with benign hypertrophy of the gland are increased difficulty in urination, less urgency and occasional retention of urine. Patients with carcinoma with chronic prostatitis manifest frequency of urination and irritation of the deep portion of the urethra.

Scholl⁴⁹ stated that pathologically and clinically there are two types of carcinoma of the prostate gland. The first is the more common type, and its degree of malignancy is lower than that of the second type. The structure is made up of cells and glands and retains the normal or glandular structure. The cells are partly differentiated and fairly regular in size and shape and retain the long, tufted end projecting into the glandular lumen, which is the most significant feature of

48. Hale, N. G.: Carcinoma of the Prostate: Early Symptoms and Diagnosis, California & West. Med. **44**:298-299 (April) 1936.

49. Scholl, A. J.: Carcinoma of the Prostate: Pathology and Prognosis, California & West. Med. **44**:298 (April) 1936.

epithelium of the prostate gland. Clinically, these prostates are large, nodular and stony and produce the symptoms of obstruction that first call attention to their presence.

The second type of carcinoma is often confused with lymphocytic infiltration. The malignant cells that have migrated into the stroma often show a streaked or etched-out appearance, in contrast to the clumped, localized disposition of lymphocytic infiltration. Clinically, the glands of this type are small, fibrous and firmly fixed. They are extremely malignant, metastasize readily and are often unrecognized, since paralysis may occur as a result of metastasis before the glands have reached sufficient size to produce symptoms of the urinary tract. Their small size often leads to the erroneous conclusion that the patients are satisfactory surgical risks and to operations, but the results are unfavorable.

Young's⁵⁰ statistics reveal that a fifth of the patients who come for relief of obstruction of the prostate gland have carcinoma, that the growth is usually in the form of a nodule or area beneath the posterior capsule in the posterior lobe and that in this position it is readily palpable by rectum and should be recognized by its marked induration. The perineum is the only route by which the diagnosis can be confirmed, and if the disease is not too extensive, a radical cure can be obtained. Cure resulted in more than 70 per cent of the cases in which the prognosis was at all favorable. Carcinoma of the prostate gland is usually unrecognized for a long time. Every physical examination should include this gland. If marked induration is present, it should cause suspicion of carcinoma. In such cases, perineal operation to expose the prostate and confirm the diagnosis should be done. If the importance of these facts would be realized, many times operation for carcinoma of the prostate gland could be performed sufficiently early for a radical cure.

Osteitis Pubis.—Lazarus⁵¹ stated that osteitis pubis is a rare complication following surgical procedures on the bladder through a suprapubic incision. The significant symptoms of this complication are pain over the lower attachments of the rectus abdominis muscles, the body, symphysis and rami of the pubic bone and the inner aspects of the thighs with spasm of the abductor muscles, so that the patient finds it painful to walk, to spread the thighs and to cough. A late symptom is pain on defecation and terminal dysuria. Fever is rarely present throughout the disease but may exist during the early stages. Symptoms usually occur in about from two to three weeks after operation.

50. Young, H. H.: Recent Work on the Prevalence of Carcinoma of the Prostate, *Tr. Am. A. Genito-Urin. Surgeons* **28**:317-329, 1935.

51. Lazarus, J. A.: Osteitis Pubis Following Suprapubic Prostatectomy, *Ann. Surg.* **103**:310-315 (Feb.) 1936.

The process rarely progresses to suppuration and the formation of a fistula. The treatment is palliative except in the few cases in which suppuration occurs. In most of the cases the condition responds to baking and massage and to the application of a properly fitted plaster cast. The disease is self-limited, with symptoms lasting from two to six months, followed by resolution and complete recovery.

URETHRA

Stone.—Traczyk⁵² described the various types of urethral calculi and the symptoms they produce on the basis of 6 illustrative cases. As a rule such calculi are solitary, the stone being a fragment of one originating in the pelvis of the kidney or a bit of débris remaining from lithotripsy. They are exceptional in females, owing to the shortness of the urethral canal, but in males they may be found alike in children and adults. The chemical state of the urine plays an important part in their formation, the lithiasis being acid, alkaline or neutral, expressing itself in the formation of urates, oxalates and phosphates. The condition of the urethra above the stone is never normal. Since the lesions are mechanically produced, the canal behind the stone dilates into a voluminous pocket. On this retrostrictural dilatation constant trauma is inflicted, associated with stagnation of urine and irritation from toxic products, which may result in diverticulosis or even in ulceration. The symptoms vary from case to case; the site of the stone is responsible for this, the tolerance of the urethra varying with the situation. Stones in the prostatic urethra cause the most pain, which is felt in the rectal, perineal or sacral regions. Incontinence is more striking if stones are at this site also. Micturition is impeded, and dribbling takes place. Diverticular calculi may remain a long time without giving any indication of their presence.

Treatment varies with the individual case, depending on the size and site of the stone and on the condition of the urethral canal. If the stone is small and only recently engaged in the anterior part of the urethra and the latter is not contracted, an attempt may be made to propel it forward by pressure exerted from behind the calculus. Occasionally it may be sufficient to ask the patient to urinate while the meatus is held closed, the jet dilating the canal enough to force the stone out. Injections of oil or cocainization of the canal combined with these maneuvers may occasionally relieve the spasm. If the stone is close to the meatus it may be liberated instrumentally by a curet or small forceps, but lithotripsy or blind extraction should never be resorted to. Removal of the stone under urethroscopic control is the only pro-

52. Traczyk, Sigismond: Les calculs de l'urètre, J. d'urolog. **41**:224-235 (March) 1936.

cedure permitting the requisite precision of action. By this means the stone can be grasped and withdrawn at the same time as the tube.

When the calculus cannot be removed in this way, recourse must be had to external urethrotomy with suture, provided there is no marked inflammation. If the stone has been arrested by a stricture, a filiform bougie left in situ from twenty-four to forty-eight hours may sometimes dilate the urethra enough to allow the stone to pass out. If this fails, internal urethrotomy is indicated, but only if the stone is movable, of small size and not associated with pronounced inflammatory lesions.

If the stone is in the prostatic urethra, an attempt should be made to push it back into the bladder with a sound. This can sometimes be done if the stone is recent. Then, if the canal is sufficiently dilated, it will be expelled easily; otherwise it can be crushed in the bladder. If it is impossible to push it into the bladder, its extraction under urethroscopic control should be tried again. If endo-urethral maneuvers fail or if the stone is large, a hypogastric incision is indicated; if the prostate proves to be an obstacle, prostatectomy can be done later.

Recurrence of urethral calculi has been reported a number of times. Such recurrence is caused almost always by strictures that have been poorly cared for, or by parts of the calculus that were left in the urethra. For these reasons it is preferable to carry out external urethrotomy, which makes it possible at the same time to section the stricture and to extract all the calculous formations within the urethra.

Diverticulum.—Kretschmer⁵³ reported a case of diverticulum of the urethra in a child 6 months of age. This lesion may occur in either males or females. In males it may be located in the anterior or in the posterior part of the urethra. In general, diverticulum of the urethra is rare, especially in children. A survey of the literature revealed reports of only 20 cases in which the diverticulum was in the anterior part of the urethra in male children.

Congenital diverticulum of the anterior part of the urethra occurs on the ventral wall of the urethra. The diverticulum is often found immediately behind the fossa navicularis and opens with a narrower or wider mouth into the urethra. The pouches vary in size from 1.5 cm. to 4 cm. by 3 cm. or 2 cm. A diverticulum of the urethra may be congenital or acquired. The congenital diverticulum is seen in the anterior part of the urethra, and in a large percentage of cases it occurs in young persons. The acquired diverticulum occurs mainly in the posterior part of the urethra, and the causes, such as urethral calculus, stricture, perforation of the urethra resulting from injuries and rupture of cysts, do not as a rule occur in childhood. The urethral diver-

53. Kretschmer, H. L.: Diverticula in the Anterior Urethra in Male Children. Surg., Gynec. & Obst. 62:634-640 (March) 1936.

ticulum not infrequently becomes the site of an inflammatory process caused by the stagnation of the urine within it and by superimposed infection. This may lead to a fistulous opening on the surface of the penis. Calculus formation may occur in a diverticulum. The obstruction to the flow of urine caused by the pressure of the filled sac on the urethral lumen leads to dilatation, infection and destruction of the upper part of the urinary tract. In some cases the diverticulum was emptied completely by pressure, only to fill again later. Although complete retention of urine is rare, this symptom was the direct cause of the patient's admission to the hospital in Kretschmer's case. The retention is mechanical in origin. The presence of the large diverticulum caused pressure on the urethra; hence complete retention followed.

The prognosis in these cases is dependent on the extent of the pathologic changes which the diverticulum has caused in the upper part of the urinary tract through obstruction and ensuing infection; this means early diagnosis and early operative intervention before the onset of irreparable injury to the upper part of the tract. When the patient is operated on before urinary stasis has caused serious harm to the upper part of the urinary tract, the prognosis is good. This is seldom the case when the operation occurs after the urinary tract has been injured. Excision of the diverticulum is the preferable treatment in this group of cases. It can be performed with relative ease and simplicity. Invagination of a small diverticulum may be tried, but as the majority of patients have large sacs, invagination is not feasible.

Stricture.—Rusche and Bacon⁵⁴ stated that stricture of the urethra which is neglected is the significant causative factor of extravasation of urine in the majority of cases. Urinary extravasation requires immediate radical operation; no palliative measures are justifiable. There are three main courses of action: diversion of the urinary stream; multiple incisions of all infiltrated areas, and, at intervals, gradual dilation of the urethra. Treatment of the stricture should be carried out later, when a process of slow dilation will produce a more satisfactory result. Suprapubic cystostomy is a satisfactory method of diverting the urinary stream. Perineal cystostomy is not desirable, as any procedure directed toward cutting the stricture at the time of the extravasation, in the opinion of Rusche and Bacon, is unwarranted.

Carcinoma.—Lazarus and Schneider⁵⁵ stated that primary carcinoma of the female urethra is of relatively rare occurrence; only 150 cases

54. Rusche, C. F., and Bacon, S. K.: Urinary Extravasation Following Urethral Stricture, *California & West. Med.* **44**:284-287 (April) 1936.

55. Lazarus, J. A., and Schneider, A. D.: Primary Carcinoma of the Female Urethra Treated by Complete Extirpation of Urethra, *J. Urol.* **35**:235-240 (Feb.) 1936.

are on record, including the case presented by them. Chronic irritation appears to be an insignificant predisposing factor. Bleeding from the urethra, difficulty in voiding and a tumor at or near the meatus constitute the outstanding symptoms of the disease. Since the majority of the patients are seen late in the development of the tumor, about a third of them present evidence of lymphatic involvement at the time of the first examination. Although several types of treatment have been advocated for this condition, it is most satisfactorily managed by complete excision of the growth, including the inguinal lymph nodes when involved, followed by thorough irradiation of the inguinal regions and site of the tumor.

Hypospadias.—Cabot⁵⁶ stated that there are certain basic requirements for a completely satisfactory operation for the cure of hypospadias. Such a procedure should completely overcome the disability; it should avoid the production of new disabilities, such as the formation of stricture at various levels or the later growth of hair within the newly formed urethra as the result of the utilization of inappropriate skin flaps; it should be sufficiently simple and certain of freedom from postoperative complications so that it can be performed with reasonable possibility of success by a well trained surgeon. At present there are in use three principles represented by three types of operation for this condition which, in their historical order of presentation, are the Thiersch and Duplay, the Bucknall and the Ombrédanne operation. The Thiersch-Duplay type of operation has been followed by some exceedingly favorable results, but is attended by many technical difficulties and is frequently complicated by the formation of a fistula. The two disadvantages of the Bucknall operation, as stated by Bucknall in his original report, were that it could not be applied to patients who have perineal hypospadias and a cleft scrotum and that it utilized skin from a hair-bearing area, which might later cause complications. The Ombrédanne operation is complicated and requires multiple stages in order to achieve a satisfactory result. Objections to it are that there is danger of formation of stricture at the junction of the posterior with the anterior portion of the plastic formation of the urethra, and, as in the Bucknall procedure, it utilizes hair-bearing areas of skin.

Cabot presented a procedure which is a modification of the Bucknall operation, by which the hair-bearing areas are avoided in the formation of the inner tube of the urethra. The skin for the formation of the inner tube of the urethra is taken from the skin of the shaft of the penis, which does not bear hair, just as in the operation of Thiersch and Duplay. The remainder of the procedure follows the technic of

56. Cabot, Hugh: An Improved Operation for Hypospadias, Proc. Staff Meet. Mayo Clin. 10:796-798 (Dec. 11) 1935.

Bucknall, in that the lateral flaps from the shaft of the penis and from the scrotum are dissected up, the penis is turned down and these flaps are united over a broad surface by the use of a quilled mattress suture. Cabot's results have shown the same freedom from formation of fistula and the same possibility of carrying out the whole procedure, it being assumed that the deformity of curvature has previously been satisfactorily corrected in two stages rather than in multiple stages, as in the original Bucknall operation. The position and caliber of the meatus can be satisfactorily planned, and freedom from a funnel-shaped opening, as well as avoidance of stricture, can be obtained with certainty.

Congenital Obstruction.—Stevens,⁵⁷ in an analysis of the results of 3,600 urologic examinations of women, stated that congenital strictures of the female urethra are common. Diaphragms or valves, in addition to several other congenital anomalies responsible for symptoms of obstruction, are occasionally found in the female urethra. The olive tip bougie, the skeneoscope and the urethroscope are the most useful instruments in the detection of urethral obstructions and should always be employed in the examination of infants and children as well as in that of adults who have symptoms suggestive of a pathologic condition of the urinary tract. Meatotomy is the procedure of choice in the treatment of this condition.

Lymphoma.—Gray⁵⁸ described the cases of 11 women with a urethral disease which was characterized by chronic urethritis with or without ulceration, which remained extremely chronic or indolent or progressed to urethral stricture or to extensive urethral ulceration. The ulceration may extend beneath the clitoris and the labia or about the introitus and to the sides of the rectum. A positive Frei reaction in 9 of these 11 patients indicated that this syndrome is caused by the virus of lymphogranuloma venereum, poorly termed lymphogranuloma inguinale.

This condition is also characterized by failure to respond to any treatment. In the cases reported antisyphilitic therapy and antimony and potassium tartrate have no apparent effect. High frequency fulguration (in 2 cases), roentgen irradiation (in 1 case) and inoculation with malaria (in 1 case) did not modify the progress of the disease. It would seem that cure of lymphogranuloma venereum results only when the patient becomes immune to the virus, as with other virus diseases. The transfer of passive immunity by injection of serum from persons with healed lesions seems to offer the greatest possibilities of cure, although few studies of this method have been made.

57. Stevens, W. E.: Congenital Obstructions of the Female Urethra, J. A. M. A. **106**:89-92 (Jan. 11) 1936.

58. Gray, L. A.: Lymphopathia Venereum—"Lymphogranuloma Inguinale"—of the Female Urethra, Surg, Gynec. & Obst **62**:745-752 (April) 1936.

TESTIS

Tumors.—Desjardins, Counseller and Gianturco⁵⁹ stated that 155 patients with tumor of the testes had been seen at the Mayo Clinic from 1920 to 1929. An analysis of these cases reveals that the majority of the neoplasms of this organ develop between the third and the sixth decade of life. In all but 2 cases the tumor was unilateral. The relation of testicular growth to undescended testis and to the influence of trauma could not be ascertained. The results of treatment were considered from the standpoint of orchidectomy alone, roentgen therapy alone and combined orchidectomy and roentgen therapy. Surgical intervention, combined with or followed by roentgen treatment, gave the most satisfactory results. This may be misleading, because none of the patients in this preferred group presented evidence of tumor for more than one year, and all were apparently free from metastasis. The patients treated by simple orchidectomy also constituted a preferred group. In the group of patients treated with roentgen rays only, the 16 patients who had died had an average survival period of eleven and four-tenths months, a period longer than that for corresponding patients in the two other groups. The impression is that patients receiving the combined forms of treatment derived more benefit than those treated by surgical methods only, or by roentgen therapy only, but in order to determine the relative value of each method by itself in comparable cases a more thorough test should be made. On the whole, roentgen treatment alone seems preferable for embryonal carcinoma, whereas for the mixed or teratoid tumor, surgical removal combined with thorough postoperative irradiation seems indicated.

Undescended Testes.—Spence and Scowen⁶⁰ reported that it has been shown that the injection of extracts of the anterior lobe of the pituitary gland into immature animals produced an increase in growth of all the tissues of the testis, and, as a result of stimulation of the interstitial tissue, enlargement of the penis and accessory genital glands. Spermatogenesis was not produced in immature mammals by means of these extracts. Similar results were obtained with extracts of the urine of pregnant women, the gonadotropic principle of which is probably derived from the placenta. It has also been shown that the injection of extracts of the anterior lobe of the hypophysis or of the urine of pregnant women causes descent of the testis in immature monkeys, in which animals they are situated in the inguinal canal.

59. Desjardins, A. U.; Counseller, V. S., and Gianturco, Cesare: Results of Treatment in Tumors of the Testis, *Am. J. Surg.* 27:71-78 (Jan.) 1935.

60. Spence, A. W., and Scowen, E. F.: The Use of Gonadotropic Hormones in the Treatment of Undescended Testes: Preliminary Report, *Proc. Roy. Soc. Med.* 28:427-435 (Feb.) 1935.

Eleven patients with undescended testes between the ages of 4½ and 15 years were treated with gonadotropic substance extracted from the urine of pregnant women. The dose used in most cases was 500 rat units injected intramuscularly twice weekly. Five of the patients had bilaterally undescended testes: During treatment both testes descended into the scrotum in 2 cases, one descended in each of 2 cases, and the position of the testes was unchanged in the remaining case. The remaining 6 patients had one undescended testis; in 3 of these the testis descended into the scrotum. Thus, 9 of 16 undescended testes entered the scrotum during treatment. The time taken to effect this change varied from two to eleven weeks. The testes which had not yet responded received treatment for from three to nine weeks. The mechanism whereby the descent is brought about is unknown. In view of the rather unsatisfactory surgical results, the authors expressed the belief that in the treatment of undescended testis a trial should be made of this form of therapy before surgical measures are considered.

Testicular Prosthesis.—Barney⁶¹ reported a case in which a testicular prosthesis was used, together with a review of similar cases presented in the literature. The various substances used for implantation included marble, glass, plaster, plaited silk, paraffin, petrolatum, vulcanite, ivory, india rubber, celluloid and silver. Paraffin, celluloid and silver seemed to be the most frequently used. The other materials mentioned seemed to have the disadvantages of weight, disintegration or infiltration by lime salts. According to Cartier, the prosthetic ball should not weigh less than 12 grains (0.87 Gm.), for if it is lighter it is likely to be drawn toward or even into the inguinal canal by muscular contraction. From his knowledge of the nonirritating qualities of silver, Barney expressed the opinion that this is the best material to use. It also has the advantage of being made into any size, shape or weight.

A testicular prosthesis has been employed for various reasons. In the days when bilateral castration was performed for the relief of prostatic obstruction, there was a demand for restoration to cosmetic perfection. In several cases the method was used after orchidectomy for tuberculosis, tumor or gonococcic or other infection. Others desired an artificial testis to fill the empty scrotum produced by cryptorchidism. In many patients there was a definite, sometimes profound, mental derangement occasioned by the half or completely empty scrotum. In all the patients it was noted that not only improvement but complete

61. Barney, J. D.: A Consideration of Testicular Prosthesis. Tr. Am. A Genito-Urin. Surgeons 28:369-373. 1935.

restoration of the normal mental status resulted a short time after operation. In his case Barney used a hollow silver ball, $\frac{7}{8}$ inch (2.2 cm.) in diameter, with thin walls.

SPERMATIC CORD

Tumors.—Thompson⁶² reviewed the literature on tumor of the spermatic cord, epididymis and testicular tunics and reported 41 cases observed at the Mayo Clinic before Jan. 1, 1935. The tumors included 26 of the spermatic cord, 13 of the epididymis and 2 of the tunica vaginalis.

A tumor of the spermatic cord sometimes attains enormous size. The largest ones are composed of lipomatous tissue in their entirety or are mixed with other tissues, forming a myxolipoma or myxofibro-lipoma. As a general rule, growth of such a fatty tumor is extremely slow. In the majority of cases the growth springs from the subserous fat around the margin of the internal inguinal ring and in enlarging grows along the inguinal canal, distending it and thus acting as a predisposing cause of hernia. When the growth is small, it is easy to distinguish at operation between the true lipoma of the spermatic cord and the more common lipoma of the properitoneal fat. If, however, the tumor is large, it is often impossible to say that its origin is not from the spermatic cord. A lipoma of the spermatic cord always should be surrounded by the tunica vaginalis communis and should derive its main blood supply from the vessels of the cord, but in time the true lipoma of the cord often will break through the tunica vaginalis communis and will connect so closely with the properitoneal fat that it appears to be of that origin. In this series of cases there were 21 cases of lipoma, in 14 of which the growth was associated with inguinal hernia. In all cases, nevertheless, the growth apparently arose from the spermatic cord, and many questionable cases were excluded. Since more than 7,000 operations for inguinal hernia were performed at the Mayo Clinic in the period covered by this review, it can be seen that the incidence is not high. Other benign tumors of the spermatic cord include fibroma, myxoma, myoma, lymphangioma, dermoid cyst and cystic tumor arising in cell rests of the wolffian body. The most common malignant tumor of the spermatic cord is the sarcoma or some combination of sarcomatous tissue with other tissue, producing a tumor which is termed myxosarcoma, liposarcoma, chondrosarcoma, fibrosarcoma or rhabdomyosarcoma.

Tumors of the epididymis occur in the proportion of 40 per cent benign and 60 per cent malignant. The fact that approximately 40

62. Thompson, G. J.: Tumors of the Spermatic Cord, Epididymis, and Testicular Tunics, Surg., Gynec. & Obst. 62:712-728 (April) 1936.

per cent are benign should be kept in mind, for there is the possibility of a favorable prognosis after surgical exploration; this should justify the surgeon in urging operation in all cases unless metastasis to other parts of the body can be demonstrated. Of the benign tumors of the epididymis, myoma and angioma are most common. Eight cases of each type have been reported in the literature in a total of 25 cases of benign tumor. One of the cases presented by Thompson is an instance of dermoid cyst, a hitherto unreported type of epididymal enlargement. Of 36 malignant tumors of the epididymis, 23 were of epithelial origin, 12 were of the sarcoma type and 1 a teratoma.

Of the tumors of the testicular tunics, those arising in the tunica vaginalis are far more common than those springing from the tunica albuginea. It is often difficult, and sometimes practically impossible, to distinguish a tumor of the tunica vaginalis from one arising in adjacent structures. For this reason, varying opinions as to the frequency of occurrence of these tumors have been expressed. A careful review of the literature discloses an approximate total of 52 cases, in 35 of which the growth may be classed as benign and in 17 as malignant. Only 4 cases of tumor of the tunica albuginea have been reported, all the growths being fibromas.

Thompson concluded from his study that approximately 70 per cent of all tumors of the spermatic cord are benign; approximately 40 per cent of tumors of the epididymis are benign and approximately 60 per cent of tumors of the testicular tunics are benign. Therefore, the prognosis is more favorable in cases of tumor of one of these structures than in cases in which tumor originates in the testis, for tumors of the testis are, almost without exception, highly malignant.

URINARY CALCULI

Higgins⁶³ reported the experimental and clinical results which have been obtained by the use of the acid ash diet with a high vitamin A content in the treatment of urinary calculi. Stones which were too large to pass spontaneously from the kidney in 23 cases were completely dissolved by this method, as indicated by roentgenographic studies and by pyelography. Seventeen patients who passed calculi at frequent intervals have been free from symptoms for more than two years since using the diet high in vitamin A.

The acid ash diet with a high vitamin A content is prescribed in addition to other therapeutic measures, such as eradication of infection and elimination of stasis. Since this regimen has been used, the incidence of recurrent stone has been reduced from 16.4 to 4.7 per cent.

63. Higgins, C. C.: Experimental and Clinical Observations on Urinary Calculi, *New England J. Med.* **213**:1007-1010 (Nov. 21) 1935.

In a period of two and a half years there has been only 1 instance of recurrent formation of stone following operative removal of lithiasis from the upper part of the urinary tract.

In another series of cases the stones diminished in size, but insufficient time has elapsed to warrant their complete solution. In other cases no decrease in the size of the calculi has been observed although the patient has followed the diet for a period of from four to five months. It is impossible to determine whether a noticeable decrease in the size of stones will occur after the diet has been followed for longer periods. It is Higgins' belief that if the stone is not producing definite renal injury and pain is not disabling the patient, conservative treatment should be attempted. If, in addition to therapeutic measures which have been used previously, a carefully planned diet is prescribed to which vitamin A is added postoperatively, the recurrent formation of stones can be reduced to a minimum.

LYMPHATICS OF THE LOWER PART OF THE URINARY TRACT

MacKenzie and Wallace⁶⁴ described a method of preparing the lymph nodes of the posterior wall of the abdomen in rabbits, which maintained the anatomic relations of surrounding structures. A series of experiments as to the part played by the lymphatics in the absorption of dye from some of the pelvic organs and the relation of the upward drainage to the kidneys was carried out in rabbits. There was no absorption from the healthy mucosa of the bladder and no marked absorption after varied forms of trauma to the mucosa of the bladder unless an acute ulcerative condition was produced. Dye injected into the wall of the lower third of the ureter passed toward the lumbar glands to the main lymphatic chain. Dye injected into the trigon, around the orifices of the ureters and around the neck of the bladder, passed to the glands at the bifurcation of the aorta through the lymphatic vessels. Breaking the continuity of the main lymphatic pathway by stripping around the termination of the aorta did not lead to the opening of subsidiary periureteral lymphatic routes but caused lymphatic edema of the pelvic organs. Tying off the lower end of one ureter leading to hydronephrosis and the simultaneous injection of dye into the wall of the bladder around the lower end of the other ureter resulted in the absorption of dye into the aortic chain as before and suggested its passage into the venous circulation to the heart and then to the kidneys. Dye injected around the renal pelvis resulted in absorption to the lumbar lymphatic chain.

64. MacKenzie, D. W., and Wallace, A. B.: *The Lymphatics of the Lower Urinary and Genital Tracts: An Experimental Study, with Special Reference to Renal Infections*, *J. Urol.* **34**:516-535 (Dec.) 1935.

UROGRAPHY

Cumming and Chittenden⁶⁵ stated that many of the inaccuracies of both intravenous and retrograde urography are well known, and the correct balance is an individual problem. Advantage must be taken of both methods, and serial or multiple exposures at carefully chosen intervals should be used to obtain the maximal amount of information. There should be not only a mutual knowledge of an entire given clinical picture but joint study of diagnostic indications, especially those afforded by urographic investigations, by both the roentgenologist and the urologist before the final diagnosis is made. It is their belief that intravenous urography has a rôle in the investigation of the urinary tract, although it is probable that the ideal medium and technic are still to be determined definitely.

Baker and Lewis⁶⁶ reported on multiple urograms as an aid in urologic diagnosis. Usually an ordinary film of the entire urinary tract is taken prior to cystoscopy. During cystoscopy catheters are passed into the pelves of the kidneys, nonobstructing catheters being used whenever possible. The catheters are then connected by means of metal adapters to syringes containing a known amount of from 15 to 20 per cent skiodan. Under direct fluoroscopic control the pelves and calices are filled by gravity. When satisfactory visualization is complete the catheters are drawn down about 8 cm. from the ureteral orifices. The roentgen ray set-up is then arranged, the catheters are withdrawn and 1 cc. of opaque medium is slowly injected into the lower part of the ureters. The first film is taken as the catheters reach the bladder. Two or three other films are then made as rapidly as possible. The time of exposure varies from one half to three fourths of a second, and the time between exposures is from eight to ten seconds. A residual film is made about ten minutes later. In cases in which ptosis of the kidney is suspected, a vertical film is taken after the last serial exposure.

The fluoroscopic part of the examination gives information which aids in determining the fixity of the urinary passages, the type of peristalsis, the relation of extra-urinary shadows, the movements of the kidneys with respiration and the passage of the medium down the ureter. The catheters are placed as high as possible, their ideal position being in the pelves of the kidneys. With practice, the roentgenologist is able to estimate accurately by the size and density of the shadow the amount of opaque medium which flows into the pelvis and calices.

65. Cumming, R. E., and Chittenden, G. E.: Intravenous and Retrograde Urography: A Comparative Study, *J. A. M. A.* **106**:602-606 (Feb. 22) 1936.

66. Baker, E. C., and Lewis, J. S., Jr.: Multiple Urograms: An Aid in Urological Diagnosis, *Radiology* **24**:177-182 (Feb.) 1935.

The entire urinary tract is included as a routine in the examination. When examination of the gastro-intestinal tract is made, more errors are caused by incomplete examination than by any other factor. Bilateral and complete examination of the urinary tract when proper methods are used is not in most instances dangerous or disturbing to the patient.

Swick⁶⁷ stated that, like other methods in medicine, excretion urography has its limitations. Despite the years of existence of cystoscopy and retrograde pyelography, these methods still have their defects. Excretion urography cannot supplant cystoscopy, retrograde pyelography and ureteral catheterization. However, excretion urography has simplified urologic diagnosis and has eliminated to a certain extent retrograde pyelography, particularly when viewed in conjunction with the history and the physical and laboratory observations. It is simpler and less taxing to subject a patient to an intravenous urographic examination first.

Excretion urography has been of considerable aid in the presence of obstructive lesions of congenital origin, or of lesions either obstructive or infectious superimposed on congenitally anomalous conditions, under which circumstances retrograde pyelography may be mechanically impossible or dangerous. In nonfunctioning hydronephrosis, the non-visualization of a conducting system incidental to the functional-anatomic derangement of the parenchyma of the kidney is of assistance as a means of localization and of diagnosis when considered together with the other clinical data. Excretion urography is well adapted to cases in which there are obscure abdominal symptoms and conditions and in which one is adverse or hesitates to subject a patient to the retrograde route of investigation. Excretion urography and retrograde pyelography should supplement rather than vie with each other as to superiority.

Hartung and Wachowski,⁶⁸ having been misled by spurious shadows in the renal region which were caused by ammonium chloride tablets, studied the absorptive capacity of the thirty-three tablets commonly prescribed. Sodium bromide, ammonium chloride and sodium bisulfate all cast dense shadows, much more in fact than pills of ferrous carbonate; the pills of ferrous carbonate have been quoted often as causing a confusing shadow.

Baretz⁶⁹ stated that the capacity of the renal pelvis must not be exceeded in pyelographic injection and that aspiration of the pelvis

67. Swick, Moses, in discussion on Cumming and Chittenden.⁶⁵

68. Hartung, Adolph, and Wachowski, T. J.: Extraneous Shadows Complicating Urography, with Special Reference to Radiopaque Pills, *J. A. M. A.* **106**:596-598 (Feb. 22) 1936.

69. Baretz, L. H.: Rupture of the Kidney Following Pyelography, *J. A. M. A.* **106**:980-983 (March 21) 1936.

should be a routine procedure to determine its capacity. To perform pyelography on a kidney which is severely infected is dangerous. Whenever possible, in the presence of acute or subacute infection, the pelvis of the kidney should be visualized by the excretory route. If the retrograde method is necessary, extreme care must be used. If there is no apparent pain or discomfort after the injection of from 15 to 20 cc., the operator should cease and visualize the pyelogram before attempting to inject any more of the medium. Pain is a constant symptom of rupture of the kidney; this may be localized or general. Nausea, vomiting, fever, chills and elevation of the pulse rate are commonly observed. There may be a diminished output of urine with the appearance of a mass in the renal area. Rigidity and abdominal distention are later signs. Tenderness over the kidney is always present. All symptoms and signs will vary with the extent of the rupture. The diagnosis is easily made on examination of the pyelogram. The extravasation may be extensive or localized to a small area perinephrically. Operation is usually indicated when the urogram shows extensive extravasation. Baretz reported 3 cases of rupture of the kidney following the indiscreet use of pyelography.

URINARY INFECTION

Helmholz⁷⁰ reported the successful use of phenylglycolic (mandelic) acid in the treatment of a 3 year old child who had considerable infection and numerous pathologic changes in the urinary tract. Reference is made to the original work of Rosenheim⁷¹ on this subject. After urologic investigation of Helmholz' patient, diagnoses of bilateral megalo-ureter and bilateral pyelitis, with right hydronephrosis and stenosis of the left ureteral orifice, were made. *Escherichia coli* was obtained on culture of the urine from both ureters. The value for blood urea was 28 mg. per hundred cubic centimeters.

Treatment with methenamine and ammonium chloride was unsuccessful; a short period on a ketogenic diet temporarily improved the infection in the urinary tract but failed to render the urine sterile. The patient also had a cyst of the brain, which was operated on. During her convalescence from this operation, treatment was instituted with phenylglycolic acid. She was given 1.25 Gm. of phenylglycolic acid neutralized with sodium bicarbonate and 0.5 Gm. of ammonium chloride four times a day. When this treatment was instituted urinalysis revealed pus, grade 3, and culture revealed innumerable colonies of *Escherichia*

70. Helmholz, H. F.: Successful Treatment by Means of Mandelic Acid of a Child with Urinary Stasis and Infection, *Proc. Staff Meet., Mayo Clin.* **11**:231-232 (April 8) 1936.

71. Rosenheim, M. L.: Mandelic Acid in the Treatment of Urinary Infections, *Lancet* **1**:1032-1037 (May 4) 1935.

coli. Treatment was continued for ten days. The p_H of the urine varied between 5 and 5.6, and the concentration of (phenylglycolic) acid in the twenty-four hour specimens of urine ranged from 0.25 to 0.43 per cent. On the eighth day of treatment the number of organisms of *Esch. coli* in the cultures of the urine was definitely reduced, and on the ninth and tenth days after the institution of treatment the cultures were sterile and the urine was crystal clear; no pus was found on microscopic examination. After discontinuation of the drugs on the eleventh day, the p_H of the urine rose to 6. Cultures of the urine made on three consecutive days after the treatment had been stopped were sterile. The patient was dismissed and will be operated on later for relief of the urinary obstruction.

URINARY CALCULI ASSOCIATED WITH DISEASE OF THE BONE

Goldstein and Abeshouse⁷² reported 14 cases of urinary calculi in association with various diseases of bones and also reviewed the literature on this subject. In 4 of their cases the condition developed after amputation of the extremities; in 2, after osteomyelitis; in 3, after fracture of the long bones; in 1, after fracture of the pelvis; in 1, after tuberculosis of the hip joints; in 1, after arthritis deformans with associated osteitis deformans, and in 2, in association with scoliosis.

A definite etiologic relationship apparently exists between urinary lithiasis and various chronic diseases of bone; consequently, in all cases of urinary calculi information concerning a previous injury or disease of the bone should be sought and carefully considered from an etiologic standpoint. The development of urinary calculi during the course of chronic disease of the bones is uncommon though not rare. Infection of the urinary tract secondary to acute or chronic infection of the bones or joints, such as arthritis or osteomyelitis, may be a predisposing factor in the formation of urinary calculi. Urinary calculi may develop after an injury of the vertebrae or cord. The formation of urinary calculi in the presence of rickets, osteitis deformans, osteomalacia, osteitis fibrosa of von Recklinghausen, osteitis fibrosa cystica associated with hyperparathyroidism and other diseases of bone appears to be dependent on a disturbance of the calcium and phosphorus metabolism which upsets the colloid-crystalloid equilibrium of the urine, with subsequent precipitation and coalescence of the urinary constituents. Careful attention should be given to providing an adequate diet in the treatment and prevention of urinary calculi of all patients, especially those with chronic diseases of the bones. A diet deficient in vitamin A

72. Goldstein, A. E., and Abeshouse, B. S.: Urinary Calculi in Bone Diseases: Review of the Literature and Report of Cases, *Arch. Surg.* **31**:943-981 (Dec.) 1935.

and in inorganic calcium and phosphorus is an etiologic factor in the formation of urinary calculi in the experimental animal and is reputed to be an etiologic factor in the clinical and experimental production of several types of chronic disease of the bones.

ULCERATIVE COLITIS FOLLOWING CYSTOSCOPY

D'Abreu and Lysaght⁷³ presented 3 cases of uremic colitis following cystoscopy. In all of them the procedure seemed justified. There was no evidence at that time that the kidneys were not functioning normally; in all 3 the examination was followed by failure of renal function and by the development of a marked degree of uremia in which symptoms of colitis were present. In 1 case the palpation by rectum of polypoid masses with ulceration led to the erroneous diagnosis of neoplasm of the rectum. Apparently this polypoid condition accompanies ulcerative uremic colitis, as it was present in both cases in which the patient died.

Cystoscopy may be a dangerous procedure; it is generally agreed that it is contraindicated in most cases of nontraumatic nephritis. In 1 of these cases subacute nephritis was present. However, this diagnosis was not made before cystoscopy, owing to the unequivocal signs and symptoms present. Necropsy in the other fatal case failed to reveal any evidence of preexistent nephritis, and the uremia was ascribed to the use of the cystoscope. In the third case, acute uremia, from which the patient recovered, occurred after cystoscopy; this patient, according to clinical and biochemical examinations, did not have nephritis.

URINARY INFECTION AND CERVICITIS

Herrold, Ewert and Maryan⁷⁴ reported that in a series of 32 cases in which the patient had an irritable condition of the bladder, there was complete relief or marked improvement in two thirds of them after coagulation of the cervix. In coagulating the cervix the heavy mucoid discharge from the cervix was dissolved and removed with caroid powder, which dried the canal and made its surface more visible. No local anesthetic was used in the cervix. A tenaculum was not used to hold the cervix in place because adequate exposure was obtained with Guttman's operative speculum. Coagulation should be done preferably between the fifth and the fifteenth day after menstruation, since complications are less likely to occur at this time. This treatment of

73. D'Abreu, A. L., and Lysaght, A. C. Uraemic Ulcerative Colitis Following Cystoscopy, *Brit. J. Urol* 7:336-344 (Dec) 1935.

74. Herrold, R. D.; Ewert, E. E., and Maryan, H. Relation of Chronic Cervicitis to Infection of the Urinary Tract, *Surg., Gynec. & Obst* 62:85-89 (Jan.) 1936.

the cervix should never be performed if acute or subacute inflammatory lesions of the internal or external generative organs are present. Coagulation with short wave diathermy was used, with the indifferent tin plate electrode placed under the patient. The spatula tip positive electrode was used for coagulation of the cervix. The proper dosage with the universal Bovie machine was obtained by setting the indicator on 40 of the coagulation meter scale, which gave the proper milli-amperage.

In cases in which the cervix appeared to be edematous and acutely inflamed, with marked lacerations, the infection was best treated first by topical applications of a 10 per cent solution of tannic acid and glycerin into the cervical canal, supplemented by daily douches of hot water. This shrank the cervix materially and reduced the activity of the chronic inflammatory process. The linear "striping" of the cervix was employed as a routine, commencing within the internal os, extending to the external os and continuing this linear striping on the cervical lips at right angles to the linear "striping" of the cervical canal. The edge of the spatula tip electrode was found most suitable. The tip is first placed firmly against the cervical tissue and the coagulation begun.

The condition of patients who had streptococcic infection was improved more than was the condition of those who had bacilluria. The urine of most of these patients was clear on macroscopic examination, and the sediment revealed bacteria but few or no pus cells. The heat-resistant so-called *Enterococcus* was the most common type of *Streptococcus* isolated in the examination and study of sediments of the urine. The infected gland-bearing tissue of the cervix was destroyed by deep crucial incisions. It is necessary that coagulation be followed by dilation of the cervical canal, including the internal os.

PAGET'S DISEASE OF THE FEMALE BREAST

WITH SPECIAL CONSIDERATION OF BIOPSY AND
PREOPERATIVE IRRADIATION

L. CLARENCE COHN, M.D.

BALTIMORE

Paget concluded from his observation of fifteen patients, each of whom presented a raw, finely granular nipple or an acute diffuse eczema of the nipple followed in one or two years by cancer of the breast, that chronic conditions of the skin of the nipple and areola are often succeeded by carcinoma of the mammary gland. He suggested and carried out excision of the involved area of the nipple and areola, but, as he himself acknowledged, too late.¹ This conclusion of Paget that the primary lesion was on the nipple and areola and that the tumor of the breast was secondary was debated in the surgical literature from 1874 until 1924, a period of forty-eight years. And Kilgore,² as late as 1921, after studying the material in the laboratory of surgical pathology of the Johns Hopkins Hospital, felt that while Paget's disease is usually primary in the nipple, in rare instances the lesion may be secondary to cancer of the breast.

This debate is not to be continued here, but I wish simply to state that the cases on which this study is based consist only of those in which the primary lesion was on the nipple or areola. At the same time I recognize that ulceration of the nipple occurs not infrequently in cases of advanced cancer of the breast associated with retraction of the nipple.

At the beginning of his studies on Paget's disease in 1907, Bloodgood³ favored Schambacher's view that the changes in the nipple and skin are secondary to the tumor of the breast. This opinion was based on the observation of cases of the advanced stage only, because in 1922, he wrote: "In the first 20 years of my experience I observed

1. Paget, James: St. Barth. Hosp. Rep. 10:87, 1874.

2. Kilgore, Olson R.: Is Paget's Disease of the Nipple Primary or Secondary to Cancer of the Underlying Breast? Arch. Surg. 3:324 (Sept.) 1921.

3. Bloodgood, J. C., in Kelly, H. A., and Noble, C. P.: Gynecology and Abdominal Surgery, Philadelphia, W. B. Saunders Company, 1907.

Paget's disease only in the late stage. I always subjected it to the complete operation. None were cured."

The emphasis of the modern conception of Paget's disease dates from Bloodgood's ⁴ article in 1924, when he presented the evidence for and the conclusion that Paget's disease of the female nipple may be a preventable disease and curable in its early stages. The evidence that Paget's disease of the nipple may be a preventable disease was based on the observation of two cases of red, granular nipple and six cases in which there was a wart on the nipple, which healed under cleansing and protective measures.

The evidence for the conclusion that Paget's disease is largely curable in the early stages was obtained from twenty cases in which operation was performed. In seven of these cases of red, granular nipple, wart and superficial ulcers, the lesion was proved on microscopic study to be benign. In nine, microscopic study revealed cancer without involvement of the axillary glands. The condition in the remaining three cases was advanced, with metastasis to the axillary glands, and belongs to the group originally described by Paget—an ulcer of the nipple, a mass in the breast and palpable axillary glands.

In one case the nipple only was removed, and cancer was overlooked in the sections. Two years later the complete operation was performed, and cancer was found in the breast and axillary glands. The patient died of cerebral metastasis one year later. This case demonstrates the danger of incomplete operation.

Paget's cancer of the nipple is comparatively uncommon. In the surgical pathologic laboratory of the Johns Hopkins Hospital, until 1924, it had been observed only twelve times in about three thousand lesions of the breast, an incidence of less than 0.5 per cent. There has been no report on Paget's disease of the nipple from the clinic of the late Dr. Bloodgood and his associates since Bloodgood's report in 1924. My intention is to present the results of additional experience since that time and especially to report on what seems to have been a remarkable, if not unique, opportunity, of observing five cases of Paget's cancer of the nipple in the last two years. From the facts brought out by the study of this new material, the following conclusions seem justified.

1. There may be no difference clinically between a small, apparently insignificant lesion of the nipple which is benign and one which under the microscope shows fully developed Paget's carcinoma. When such a lesion does not heal in a few weeks by simple cleansing and protective measures, a biopsy should be performed.

4. Bloodgood, J. C.: Paget's Disease of the Female Nipple: A Preventable Disease, Curable in Its Early Stages; a Study of Thirty Cases, *Arch. Surg.* 8:461 (March) 1924.

2. The biopsy for a lesion on the nipple should consist of complete excision of the nipple, the areola and the central zone of the breast beneath.

3. Fully developed cancer of the nipple may be present without the presence of a fissure or an ulcer. There may be only slight keratosis surrounded by an area of irritation, the entire apparently innocent lesion being confined to the nipple only.

4. When microscopic study of the sections made from the tissue removed for biopsy shows Paget's carcinoma, operation for complete removal of the breast should follow.

5. There is apparently no danger in delaying the complete operation after biopsy of the type described in order to carry out thorough pre-operative irradiation of the supraclavicular area, axilla and breast.

6. When an ulcer on the nipple is associated with a palpable mass in the breast or with palpable axillary glands, there is no danger in delaying the complete operation for one course of preoperative irradiation. There is nothing to be gained by biopsy in such cases.

7. There seems to be a distinct danger in irradiation of an apparently insignificant lesion of the nipple without performing a biopsy previously, unless this irradiation is to be followed by a complete operation, because an ulcer which is the seat of cancer may heal over entirely under irradiation, leaving the cancer in the breast and the axillary glands unobserved. There is one exception to this statement, which will be noted later.

8. The restriction of the operation to the excision of the nipple, areola and central zone of the breast beneath is justified only on the basis of expert pathologic knowledge, and if there is doubt as to whether the lesion is malignant while the sections are being submitted for the opinion of others, there should be irradiation.

9. Sufficient time has not elapsed to allow any conclusion as to the increase, if any, in the percentage of cures by the addition of preoperative irradiation, but sufficient evidence has accumulated to allow me to say that there is apparently no danger in delaying the complete operation for preoperative irradiation.

BENIGN LESIONS OF THE NIPPLE

From 1925 to 1935, inclusive, there were examined in this clinic fifty-eight patients with lesions of the nipple or areola, and of these, forty-nine had benign and nine malignant lesions (table 1). Sixteen of the forty-nine with benign lesions were subjected to operation, and thirty-three were not (table 2). Before taking up the nine cases of cancer of the nipple, I want to consider the benign lesions in some detail. In the group of thirty-three patients who were not operated on there were twenty-four with uncomplicated keratosis of the nipple which healed

quickly when simple cleansing and protective measures were employed. There was one patient whose nipples were sore, but there was no keratosis or other apparent lesion, and the soreness disappeared after the institution of treatment such as is given for keratosis. In three instances the keratosis of the nipple was complicated by the presence of a superficial ulcer or a small fissure, and in these three instances there was complete healing.

The condition in these three cases did not differ clinically in any respect from that in the four in which the nipple and areola were excised for diagnosis, except that the lesion healed quickly under treatment with soap and water, alcohol and petrolatum. Twice warts on

TABLE 1.—*Incidence of Lesions of the Female Nipple (1925 to 1935, Inclusive)*

Type of Lesion	No. of Cases
Benign lesions.....	49
No operation.....	33
Operation.....	16
Malignant lesions.....	9
Clinically malignant.....	4
Clinically questionable.....	5

TABLE 2.—*Incidence of Operation for Benign Lesions of the Female Nipple (1925 to 1935, Inclusive)*

Condition	No. of Cases
No operation.....	33
Uncomplicated keratosis.....	24
Sore nipples, no keratosis.....	1
Keratosis and superficial ulcer or small fissure.....	3
Warts.....	3
Papilloma of areola.....	2
Operation.....	16
Keratosis and ulcer or fissure or red granular nipple.....	4
Retraction of nipple with wart or red granular nipple.....	7
Benign adenoma of nipple.....	2
Infected dermoid cyst of areola.....	1
Fibroma of areola.....	2

the nipple were observed to heal under the same cleansing and protective measures. In these instances the warts were confined to one nipple. In another case a wart occurred on each nipple.

A woman 21 years of age was first seen at the clinic on Feb. 20, 1933. There was a diffuse wart on each nipple associated with congenital retraction of the nipple. The condition had been present for five years. Under cleansing and protective measures there was distinct improvement during the subsequent four weeks that the patient was observed. She was then lost from observation until Nov. 27, 1935, when she returned as a result of the follow-up card. The warts were just as distinct as when I first examined her in February 1933, two years and nine months before. As she had neglected the treatment prescribed during this interval, it was tried again for two months, and as there was no improvement the patient

was referred to Dr. Neill for radium treatment on Jan. 23, 1936. The examination on March 25 showed marked improvement in the warty condition of both nipples, but the warts have not yet completely disappeared.

The irradiation in this case for an apparently benign lesion was given because of the age of the patient and the bilateral involvement.

In the remaining two cases in which operation was not performed papilloma of the areola was present, which apparently is not an etiologic factor in cancer of the nipple and areola.

Of the sixteen cases in which at operation the lesion was diagnosed as benign in the frozen section, there were four in which keratosis



Fig. 1—Low power photomicrograph of a section through a nipple showing Paget's carcinoma. This case is the earliest example of this condition at the clinic. Excision of the nipple and areola was done on Jan. 13, 1926. Complete operation for cancer was performed two years later. Death occurred five and one-half years after excision of the nipple, from metastasis.

was combined with an ulcer, a fissure or a red, granular nipple and the lesion failed to heal under treatment, and yet microscopic study in three still showed a benign ulcer. Irradiation was not done in these three cases, and no operation other than the excision of the nipple, areola and central zone of the breast was performed. There has not been a recurrence in any of the cases.

The lesion in the fourth case was also diagnosed as benign, but it has been reported that the patient died five and one-half years later

from cancer of the same breast and that two years before death a complete operation had been performed.

A restudy of this case shows Paget's cancer in the sections taken for biopsy. It is the earliest example of Paget's carcinoma of the nipple at the clinic, and evidence would indicate that the patient would have been cured had the disease been recognized at the time of the biopsy and a complete operation performed (figs. 1 and 2).

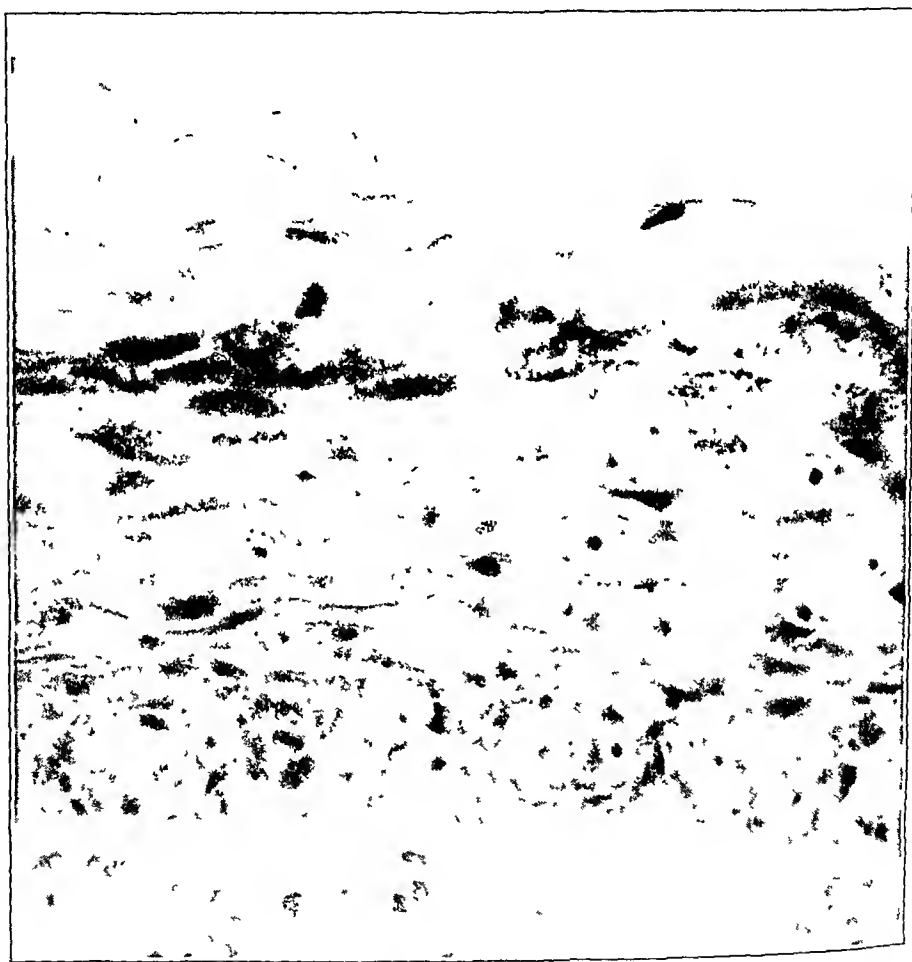


Fig. 2.—High power photomicrograph of the section shown in figure 1. The large cells are malignant although still confined to the epidermis.

There are seven cases in which there was retraction of the nipple, associated with a wart, an ulcer or a red, granular nipple, and in six instances the microscopic picture was distinctly benign. In one case there was a disagreement among those who studied the sections as to whether the lesion was malignant. This patient was given two courses

of irradiation but was not subjected to the complete operation, and she was well when last examined in September 1935, five months after operation.

In one instance a patient with cancer of the breast had a red, granular nipple on the opposite breast associated with a wart, and at the time of the operation on the cancerous breast I also excised the nipple which was the seat of the wart. This case must be eliminated from any study of the ultimate results, as the patient died in two years from cancer primary in the opposite breast.

There is one case in the group of instances of benign lesions in which operation was performed which I wish to report a little more in detail, because it was unique in my experience until 1927, when the patient came under observation.



Fig. 3.—Photograph showing a large nipple with a large benign adenoma beneath. The clinical diagnosis was Paget's cancer. Complete operation without exploration was performed on Oct. 18, 1927. There was no metastasis to the glands. The patient was well in February 1936. For the photomicrograph made in this case see figure 4.

Mrs. W., aged 40, the mother of four children, was examined by me on July 5, 1927. The examination revealed a very large, red nipple in which there were two sinuses. The red nipple was surrounded by a blue zone, and between the red and the blue zone there was a line of demarcation. This nipple was firm, hard and very tender. It had been in this condition for one month. At first there was a crust, and when the crust came away the two sinuses appeared (fig. 3).

In 1911, sixteen years prior to my examination, before the patient's marriage, Dr. Bloodgood had excised a benign papilloma of the nipple, and there is a note that at this time the nipple was harder and more prominent than the opposite nipple (left). When the patient nursed her first child she had a great deal of trouble with the right nipple, but if there was lactation mastitis there was no abscess, and there was less trouble during subsequent lactations.

She was given cleansing and protective treatment to the nipple, and disappeared from observation from July 5 to Oct. 13, 1927, during which period she was under the care of her family physician

On Oct. 18, 1927, I performed a complete operation without biopsy or exploration. The glands were not involved, and there was no evidence of cancer in the nipple or in the breast. There was, however, a large benign adenoma just beneath the nipple, which could easily have been recognized in the gross and in the frozen section had I first excised the nipple and areola with a zone of the breast beneath (fig 4). The patient is now well (January 1936), but she could have been saved the complete operation had I been familiar in 1927 with this type of benign adenoma of the nipple which presents the clinical appearance of Paget's cancer

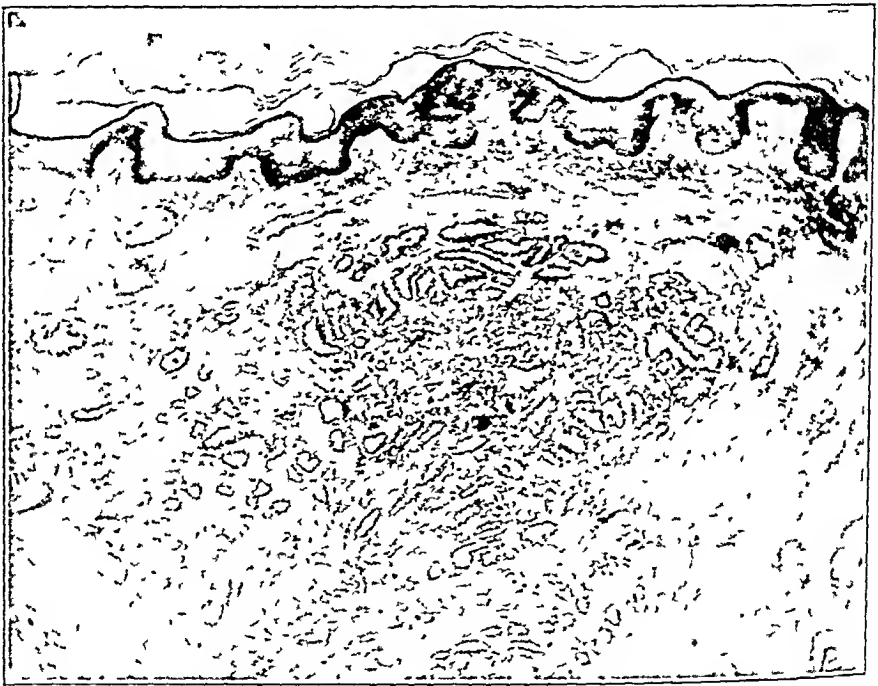


Fig. 4—Low power photomicrograph of a section of the benign adenoma of the nipple shown in figure 3.

There is only one similar case in this series, and the patient is well more than eight years after excision of the nipple, areola and central zone of the breast only (figs. 5 and 6). Three other cases—infected dermoid cyst of the areola and two cases of fibroma of the areola—neither of any special significance in this study, complete the list of sixteen cases of benign lesions of the nipple and areola in which operation was performed.

Recently, a patient aged 53, in whom I excised the nipple, areola and central zone of the breast for retraction and irritation of the nipple of one year's duration, which on microscopic study proved to be benign, remarked: "If women only knew that when they had trouble

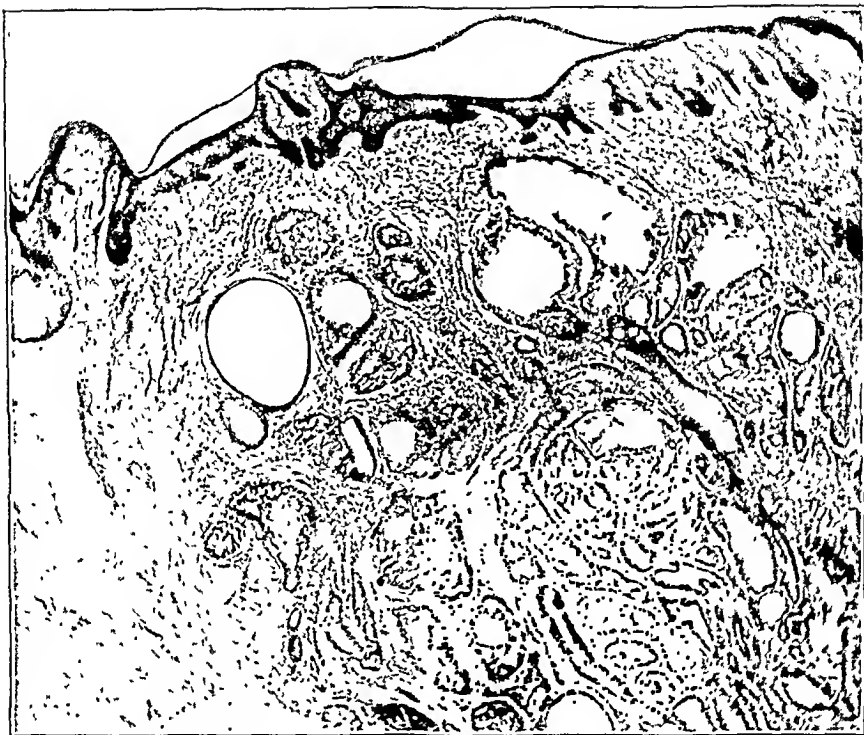


Fig. 5.—Low power photomicrograph of a section through the nipple in a case of benign adenoma of the nipple. Excision only of the nipple and areola and the central zone of the breast beneath was performed in September 1928. The patient was well in February 1936.



Fig. 6.—High power photomicrograph of the section shown in figure 5.

with the nipple they would not necessarily loose the entire breast they would consult their doctors sooner." This statement seems to be the secret of the prevention and cure of Paget's cancer of the nipple, and physicians must see to it that this statement is disseminated. It is my opinion that one is justified in even going a step further and stating that if women consult their physicians immediately when they notice something unusual on the nipple, or have an itching sensation on the nipple, the large majority not only will not loose the breast but will not even loose the nipple.

A study of the duration of symptoms in the group of cases of benign lesions in which operation was performed shows an average duration of symptoms of almost two years (twenty-two months). In the twenty-four cases of uncomplicated keratosis in which the operation was not advised, in the majority of instances the keratosis had not been noticed by the patient, but was found on examination. From this it seems that women are not quite as alert about an area of keratosis on the nipple as they are about a similar area on the skin of the face and that it might be a good plan for physicians to emphasize to women the importance of inspection of the nipples for keratosis and other lesions rather than to delay until symptoms appear.

PAGET'S CANCER OF THE NIPPLE

Of the nine cases of fully developed Paget's cancer of the nipple observed during the last eleven years, five have been observed during the last two years, and in this period there have been a total of three hundred and sixty-three cases of lesions of the breast, making the incidence of Paget's cancer in the past two years 1.3 per cent. In four of the nine cases the lesions were clinically malignant and in five clinically questionable. In the latter group the diagnosis was settled by biopsy. I wish to report these nine cases in detail.

Clinically Malignant Lesions.—Reports of the four cases in which the lesion was clinically malignant follow:

Mrs. S. E., aged 77, was seen at the clinic on Jan. 25, 1927. For from six to nine months there had been what she considered to be a fever blister on the lower part of the right nipple. There had been intermittent healing followed by recurrence and at times a little bleeding. A scab would form and fall off, leaving a red area exposed. Two months before she was seen she noticed a lump in the breast. The examination showed a small area of ulceration on the lower half of the nipple, with weeping, a palpable mass in the center of the breast larger than a silver dollar and palpable axillary glands. A roentgenogram of the chest showed no evidence of metastasis. On January 26 Dr. Bloodgood performed a complete operation, using local anesthesia. The sections from the nipple, the tumor in the breast and the axillary glands showed cancer (figs. 7 and 8).



Fig. 7.—Gross specimen from a complete operation performed by Dr. Bloodgood on Jan. 26, 1927. The photograph shows a small area of ulceration on the lower half of the nipple. Death occurred one year and five months after operation from an unknown cause.



Fig. 8.—Gross section through the specimen shown in figure 7, showing gross cancer in the center of a fatty breast.

The patient died on June 15, 1928, one year and five months after operation. No accurate information as to the cause of death could be ascertained.

Mrs. M., aged 45, was seen on March 9, 1934. She was the mother of five children, the oldest of whom was 23 years of age and the youngest 7 years of age. She was menstruating normally. The left nipple was almost entirely destroyed, and surrounding the site of the nipple for an area the size of a 25 cent piece there was superficial ulceration and scabbing (fig. 9). There was no distinct mass just beneath the nipple, but in the midzone of the upper hemisphere of the breast there was a mass 6 cm. in diameter, over which the skin dimpled when the breast was raised forward. There was "pig skin" over the lower hemisphere of the breast, suggesting a lymphatic blockade; I was unable to palpate any glands in the axilla, but there was tenderness in the axilla on pressure. Transillumination of the breast showed a dark area at the site of the palpable mass in the upper hemisphere, but the breast beneath the nipple was clear (fig. 10).

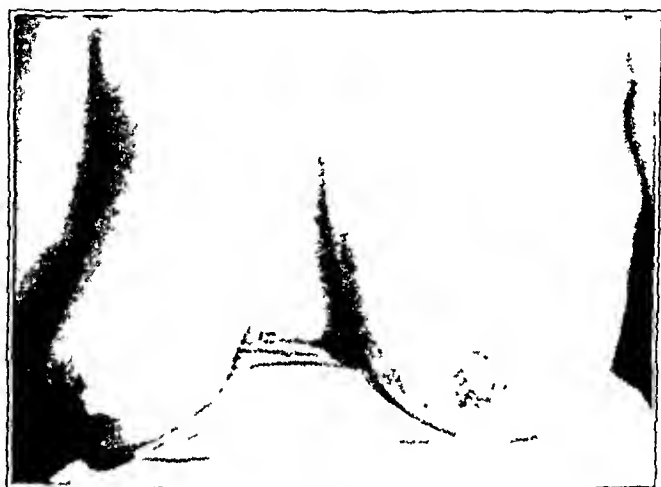


Fig. 9.—Photograph showing almost complete destruction of the left nipple with superficial ulceration and scabbing. Complete operation was performed on March 13, 1934, without preoperative irradiation. Death occurred on July 12, 1934, from metastasis.

Scabs had been present around the nipple for two years before examination, and although the patient sought medical advice at the onset and was given some local medicine, she did not again seek medical attention until one week before she entered the clinic. The mass in the breast had been present for one year, but the pig skin, which she called "goose skin," had been present only two weeks. Why I did not give preoperative irradiation I do not know, and there is no note that preoperative irradiation was ever discussed. In view of my experience now the patient should have been given the benefit of preoperative irradiation. I did the complete operation without biopsy on March 13, 1934, removing a large circular zone of skin about 16 cm. in diameter. There was metastasis to the base, middle and highest apex axillary glands and metastasis to the glands in the subscapular fossa. A roentgenogram of the chest taken on July 7, 1934, showed metastasis, and the patient died on July 12.

Mrs. M., the wife of a physician, was examined by Dr. Bloodgood and Dr. Stewart and myself on Jan. 2, 1935. She was 37 years of age and had one child, 9 years of age. Itching of the left nipple had been present for eleven months, and for ten months she had noticed a red area of irritation on the nipple (fig. 11). She and her husband had noticed a mass in the breast for six weeks.

On examination we found a crescent-shaped, red, granular area on the left nipple, subdued transillumination of the left breast and two palpable masses in the breast and a palpable gland in the base of the axilla. Roentgenograms of the



Fig. 10.—Photograph taken during transillumination of the breast shown in figure 9.



Fig. 11.—Photograph showing a red, granular left nipple.

chest, pelvis and skull showed no evidence of metastasis. Dr. Henry K. Pancoast, of Philadelphia, gave the preoperative irradiation, and on March 7 Dr. Floyd E. Keene, of Philadelphia, performed a complete operation. He found extensive metastasis to the axillary glands (figs. 12, 13, 14 and 15). After the operation there was further irradiation. Dr. Keene reported that the patient died on August 6, five months after operation, and that at autopsy there was extensive metastasis to the liver and peritoneum.

Miss L., aged 54, was referred to the clinic by Dr. Lillian E. Shaw, of Harrisburg, Pa, on Oct. 11, 1935. There was a scab on the right nipple, and



Fig. 12.—Low power photomicrograph of a section through the nipple shown in figure 11. A small nest of residual cancer buried in granulation tissue is seen.



Fig. 13.—High power photomicrograph of an area of the cancer shown in figure 12.

the nipple had practically disappeared (fig. 16 *A*). On transillumination the right breast was a little darker than the left, and around the scab there was a little induration of the areola. There was also an area of induration in the upper, outer quadrant of the right breast about the size of a silver dollar, but there were no palpable glands in the axilla. A roentgenogram of the chest was normal.

One year before her coming to the clinic the patient's attention was called to the right nipple by itching, and the itching directed her attention to the presence of a crack on the nipple; later a crust formed on the crack. Although Dr. Shaw

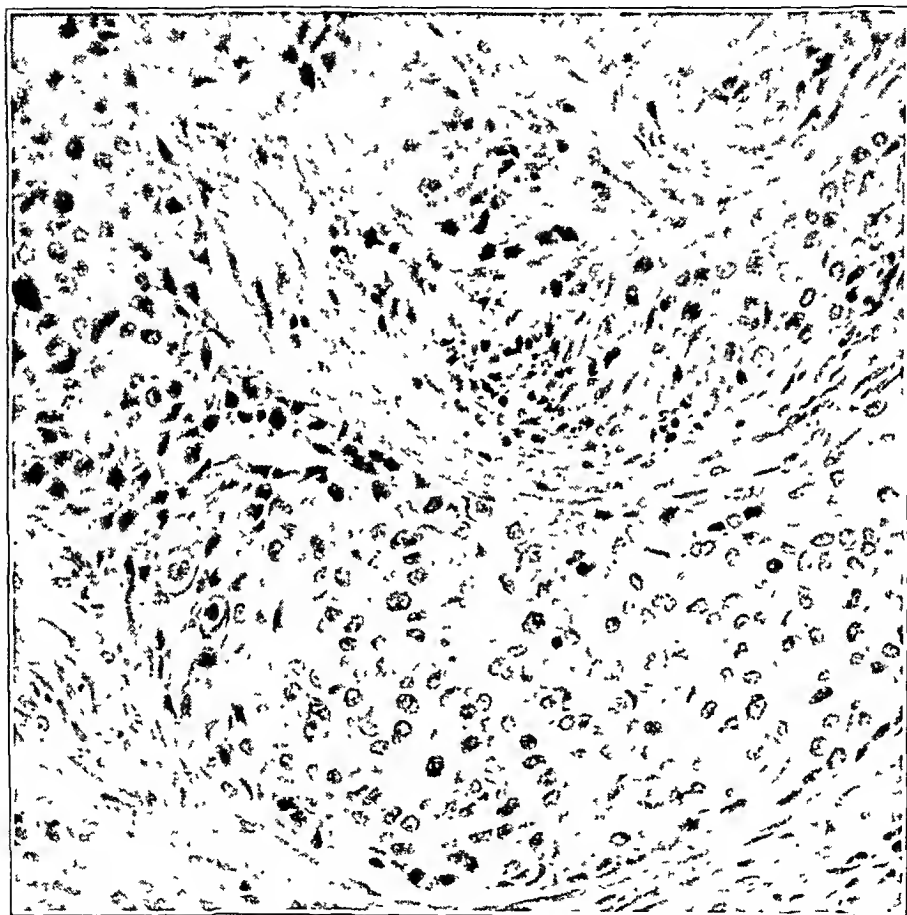


Fig. 14.—Low power photomicrograph of a section of the tumor of the breast shown in figures 12 and 13.

saw her and advised treatment a number of months before the present examination, she delayed because all sensations in the nipple disappeared and only a scab remained. In the fall of 1935 she noticed that the scab was a little larger, and for two weeks there had been pain in the breast, which had never been present before. I referred her to Dr. A. Z. Ritzman, of Harrisburg, for preoperative irradiation. She volunteered the information that during the first week of

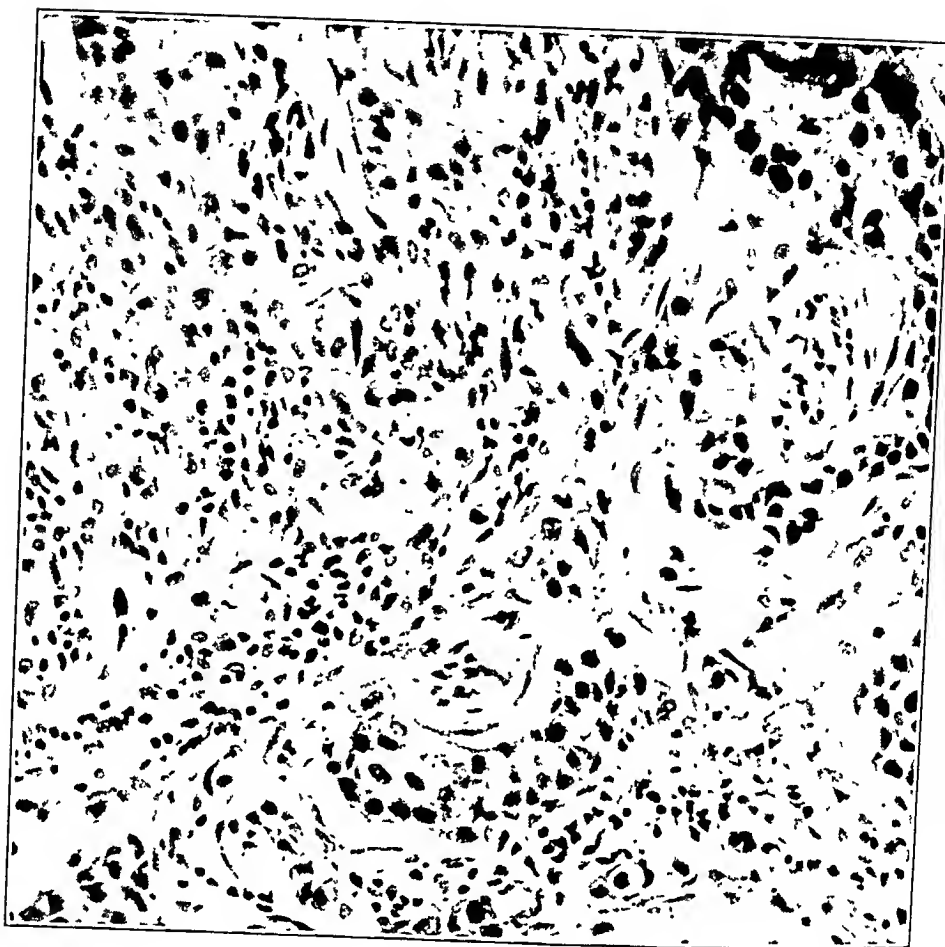


Fig. 15.—Photomicrograph of a gland from the axilla showing cancer. This photograph and figures 11, 12, 13 and 14 were made in the same case.

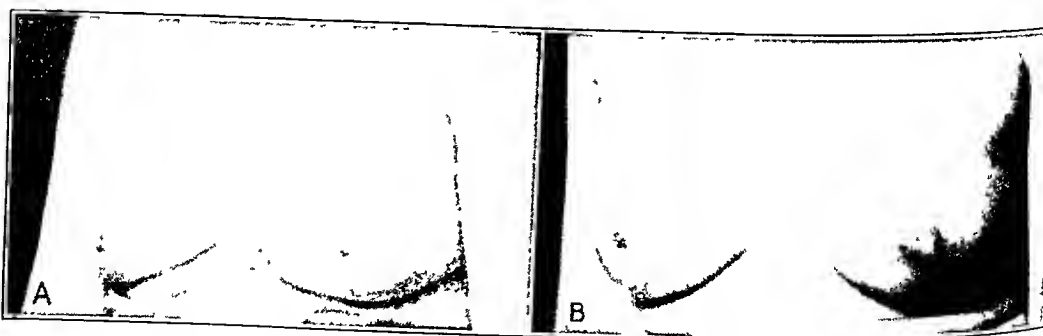


Fig. 16.—*A*, photograph showing a scab on the left nipple and destruction of the nipple. The photograph was taken before irradiation. *B*, a photograph taken after irradiation.

the irradiation the scab disappeared, leaving an open wound which discharged some material for about ten days.

When I examined her on November 16, one week after the irradiation was completed, there was epithelitis over the breast, axilla and supraclavicular area. There was no crust or ulcer on the nipple, but the areola was about twice the size of the opposite areola, with complete disappearance of the nipple. The site of the nipple was healed over completely (fig. 16*B*). There was still a distinct difference between the two breasts on transillumination and palpation.

I performed a complete operation on December 27. The section through the nipple at the site of the healed ulcer showed no evidence of carcinoma. Sections

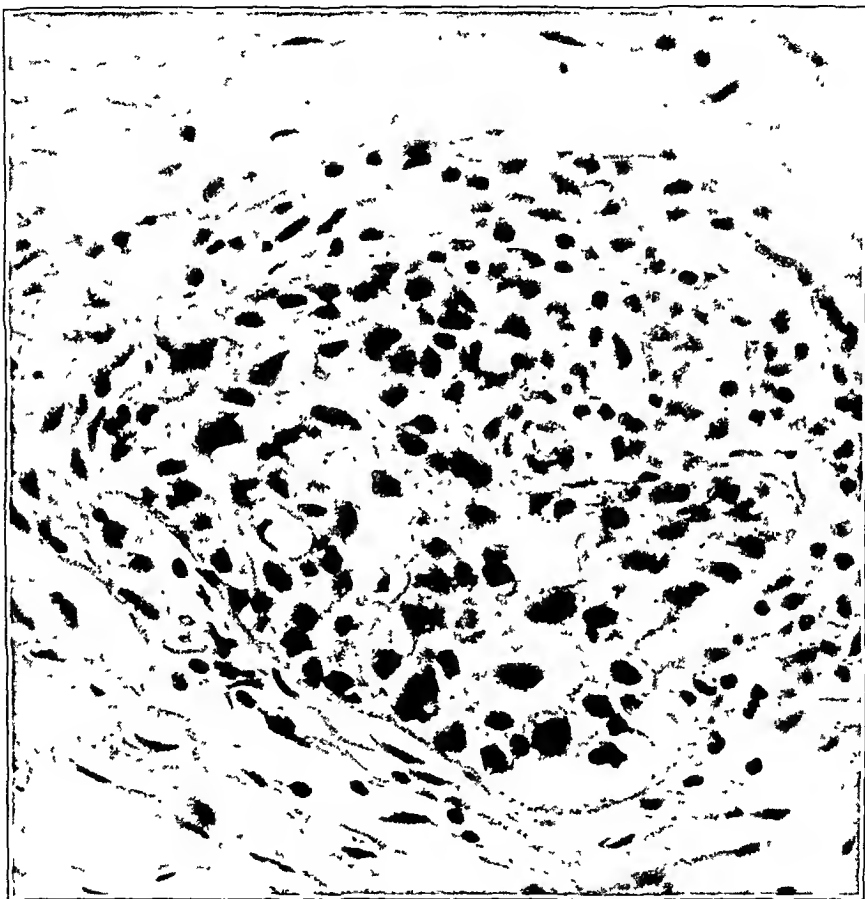


Fig. 17.—Low power photomicrograph of a group of cancer cells in the breast beneath the nipple after preoperative irradiation.

from the breast beneath the nipple showed distinct microscopic evidence of cancer, but only a few little islands of cancer surrounded by lymphoid cell granulation tissue (fig. 17). In another section through the breast at some distance from the nipple there was another small island of cancer.

Sections through the base, middle and highest apex axillary glands showed no metastasis. Dr. Gey was unable to grow the cancer cells in tissue culture.

Of these four patients who in addition to an ulcer of the nipple had a mass in the breast, three are dead, one year and five months, five months and five months, respectively, after operation. Judging from the tragic results in the three cases, the outlook in the fourth and very recent case would seem to be anything but hopeful. But I believe that the contrary is true and that as the axillary glands show no metastasis the patient's chances of remaining well and free from recurrence for five years are at least 70 per cent.

Of the three patients who are dead, one was given preoperative irradiation and two were not. As the chances of curing a patient with Paget's cancer of the nipple associated with a palpable mass in the breast by surgical measures alone are so small there seems to be no danger in the additional delay necessary for thorough preoperative irradiation (table 3).

Clinically Questionable Lesions.—It is the series of five cases in which the visible and palpable lesion was confined entirely to the nipple

TABLE 3.—Results of Operation for Malignant Lesions of the Female Nipple
(1925 to 1935, Inclusive)

	No. of Cases
Clinically malignant lesions.....	4
Death from 4 to 17 months after operation with internal metastases	3
Living and well (recent case, 12 months).....	1
Preoperative irradiation	2
Clinically questionable malignant lesions.....	5
Death more than 5 years after operation, cause unknown..	1
Lost from observation.....	1
Living and well from 1 to 5 years.....	3
Preoperative irradiation	2

without any clinical evidence of involvement of the breast or axilla which brings to light some interesting observations. In the first place, when the ultimate results in these five cases are compared with the ultimate results in the group of cases in which the lesion was clinically malignant, one finds an entirely different state of affairs. In the former five cases, three of the patients are living and free from recurrence for periods of five years, two years and one year since they came under observation. One patient was followed for five years, at which time she was free from recurrence, and then she was lost from observation. The fifth patient was well in June 1932, three and one-half years after operation, when last examined by her physician. Since this time she has been lost from observation.

It is evident even from such limited statistics that if any large percentage of patients with cancer of the nipple are to be cured they must be seen in the early stage and that both the patient and the phy-



Fig. 18—Photograph showing a red, granular nipple with superficial fissure. Biopsy was followed by immediate complete operation on Aug. 15, 1927. Metastasis to the highest apex axillary gland occurred. No preoperative irradiation was given. The patient was well for five years and was then lost from observation.

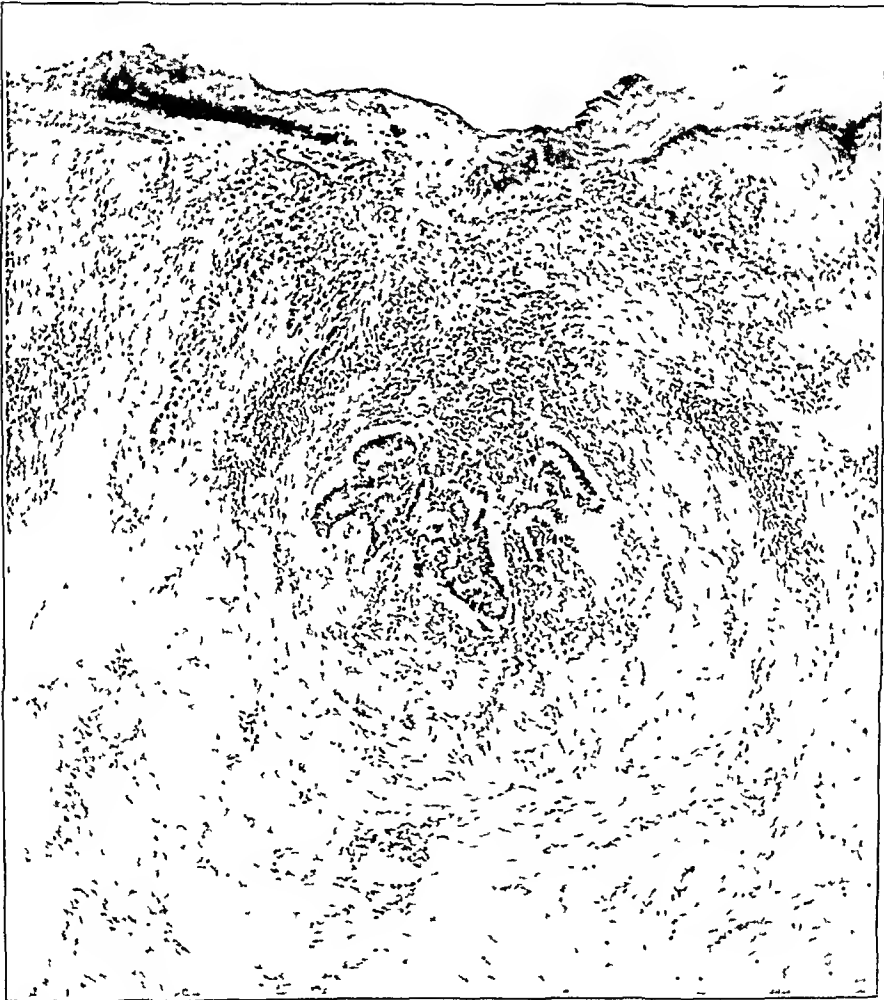


Fig 19—Low power photomicrograph of a section through the nipple shown in figure 18. In spite of these early changes in the nipple and in spite of the fact that there was no palpable mass in the breast or microscopic evidence of cancer in the breast beyond the nipple zone, there was metastasis to the highest apex axillary gland.

sician must realize that the same attention should be paid to any irritation of the nipple in women who are not nursing children as in those who are.

On May 13, 1927, Mrs. B., aged 39, was seen at the clinic because of a watery oozing from the left nipple, of four months' duration. She was the mother of four children, the youngest of whom was 4 years of age. During the time she was nursing the child who was 6 years of age at the time of her admission to the clinic this same breast became sore and was very much enlarged and hard, and the nipple was sore. After she took the baby away from the breast for several days and applied some salve, the condition cleared. She put the baby back on the breast, and there was no further trouble until the onset of the present condition.

At the first examination there was a scab on the nipple, and this came away after the first application of petrolatum, leaving a superficial fissure on the nipple (fig. 18). Under treatments with soap and water, alcohol and petrolatum the nipple almost healed by June 9, a period of three and one-half weeks, and completely healed after the ulcer was treated with phenol followed by alcohol. However, the ulcer recurred in twelve days, and entirely healed for the second time by July 25, and recurred for the second time one week later.

In view of these recurrences of the ulcer, which was still only a minute superficial fissure, 3 mm. in diameter, I decided to operate. At the operation, on August 17, I excised the nipple and areola with the central zone of the breast beneath, using the endotherm needle. Frozen sections made immediately showed fully developed Paget's carcinoma, and after packing the wound with gauze wrung out of a 50 per cent solution of zinc chloride, I closed it hurriedly with silver wire and did a complete operation (figs. 19 and 20). The axillary glands were involved, and the section of the highest apex gland showed metastasis (fig. 21). No gross or microscopic cancer in the breast was observed beyond the microscopic involvement in the area of the nipple. Even though the patient's chances for remaining well and free from recurrence for five years were at most 10 per cent, she was living and well in 1932, after five years, and later was lost from observation.

When one considers that in this case there was a delay of more than three months between the first examination and the operation and that at operation cancer was found, with involvement of the glands, I feel that I postponed the operation for too long a period. I did this because the ulcer healed on two occasions. However, the ulcer did not heal under treatment with soap and water and alcohol and petrolatum alone, as phenol was added. I decided at this time never again to use phenol on an ulcer of the nipple, because there was definite proof that Paget's cancer of the nipple healed over under this treatment. I also decided at this time never to use radium or roentgen rays on the nipple, for I felt that this too might produce superficial healing. It was eight years before I had an opportunity to prove this. In the case of Miss L. this idea has been confirmed. Because of these two observations I believe that it is justifiable to state that there is a distinct

danger in masking the diagnosis if more than simple cleansing and protective measures are employed in an attempt to heal an ulcer on the nipple, no matter how superficial and apparently benign the ulcer appears. Definite proof of how long one is justified in using these simple measures before doing the biopsy has not been found, but an arbitrary time of three weeks is chosen. When the ulcer on the nipple is associated with a mass in the breast or with palpable



Fig. 20—High power photomicrograph of an area of the section shown in figure 19.

axillary glands, preoperative irradiation is given, with the distinct understanding that the complete operation is to follow, regardless of whether or not the superficial ulcer heals.

The following case, that of Mrs. F, again demonstrates the danger of irradiation as a first treatment for a clinically benign lesion of the nipple.

A white woman, aged 55 was seen on Jan. 25, 1929, with the history of irritation of the nipple associated with a watery discharge from the nipple, both of which had been present for one year and nine months. She said at the beginning that the nipple had itched and that later it became scaly. She had consulted her surgeon in July 1928, six months previously, without telling him she had been given roentgen treatment to the nipple. Her surgeon prescribed a little petrolatum and cleanliness, and when he saw her one month later the nipple was

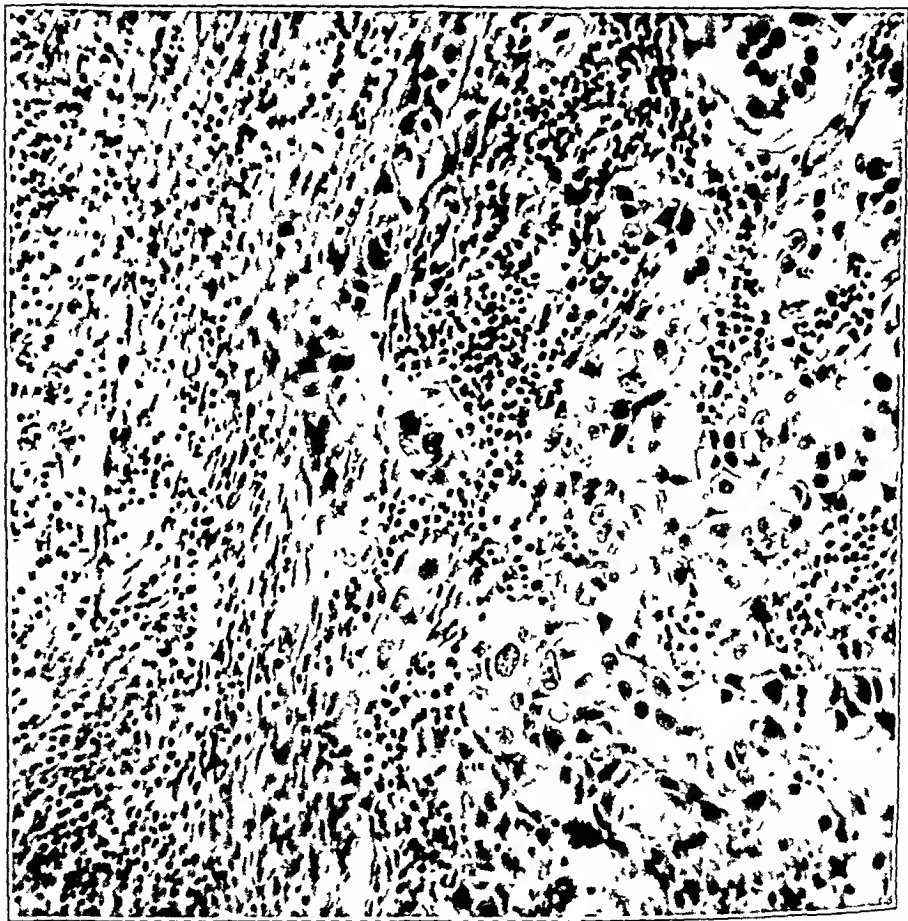


Fig. 21.—Photomicrograph of the highest apex axillary gland, taken in the same case as figures 18, 19 and 20.

normal, but when he examined her on Jan. 24, 1929, there was a line of nodules beneath the nipple and enlarged axillary glands, both of which were absent on his two previous examinations.

At the operation on February 1 Dr. Bloodgood excised the nipple and areola and the breast beneath, and as the frozen sections showed cancer he closed the wound and did a complete operation at once. Although the glands were palpable before operation, sections did not show metastasis. There was, however, cancer in the breast beneath the area excised at biopsy. The patient was well when

last examined by her physician in June 1932, three and one-half years after operation.

Mrs. R., aged 54, was first seen at the clinic on Sept. 24, 1930. She was the mother of three children, the oldest being 37 years of age and the youngest 21 years. The left nipple was of the red, granular type, with superficial ulceration of the nipple and areola. Transillumination of the breast was clear, and no mass could be made out in the breast or axilla on palpation. The left nipple had been retracted for thirty-seven years, dating from a caked breast at the time of the first lactation. One year before coming to the clinic the patient noticed a little secretion from the nipple and then a scab. Under the applications of zinc oxide ointment the scab has been appearing and disappearing. For three months, under some type of light treatment, the lesion dried up and then appeared again. On September 26, I made the usual biopsy, and as the frozen sections showed cancer, I followed this at once with a complete operation. There was no involvement of the breast beyond the zone of the nipple or of the axillary glands. The patient's daughter reported on Sept. 6, 1935, that her mother was well.

The following two cases, which will be reported in detail, are the two cases observed in the last two years in which the lesion was apparently confined to the nipple only, and in each case the nipple, the areola and the central zone of the breast beneath were excised for biopsy. In each case the sections showed Paget's cancer, and in each case pre-operative irradiation to the breast, axilla and supraclavicular area was done, followed by a complete operation. In both instances residual cancer was found in the breast, but in neither instance was there metastasis to the axillary glands, nor did Dr. Gey obtain any growth of tumor cells in tissue cultures. These two patients are both well, but it is less than two years since the first one has been observed.

Mrs. B., aged 31, first came under observation on Jan. 5, 1934. The left nipple had been replaced by an ulcer, and on transillumination there was a dark area beneath the nipple the size of a 25 cent piece. The remainder of the breast was clear on transillumination, and there was no palpable mass in the breast or the axilla. Her one child was aged 15 years, and she remembers having a little trouble with this breast during lactation. In 1929, five years before coming under observation, there was acne of both breasts, which was not confined to the nipples but was all over the breast. She was given a salve for the acne, and after the acne disappeared there was itching and then a tiny crack on the left nipple. The crack became covered with a scab which would come and go. The patient went from 1929 to nine months before she came to the clinic before consulting a physician. When she consulted her physician because the nipple was sore she was given a powder and petrolatum to apply. Six months before her coming to the clinic another physician gave her a course of roentgen treatment, after which the ulcer would heal and then break down. In another clinic two months previously a small section was taken for biopsy and operation was advised.

On Jan. 5, 1934, the nipple, the areola and the central zone of the breast beneath were excised at the clinic. The sections showed Paget's cancer (fig. 22). The patient would not consent at this time to a complete operation. She was given irradiation at the Kelly Hospital under Dr. Neill. This was com-

pleted in February (fig. 23). She was observed frequently during February, March and April, and although there was no evidence of any remaining disease in the breast or axilla, Dr. Neill gave a second course of irradiation during the latter part of April and the first part of May. She was examined frequently



Fig. 22.—Low power photomicrograph of a section through the nipple, which was excised on Jan. 6, 1934. Fully developed Paget's cancer is shown.



Fig. 23.—Photograph taken on March 24, 1934, two months after biopsy, showing the extent of the excision. The microscopic section is shown in figure 22.

during June, July, September and November, and on Nov. 23, 1934, I excised a nodule smaller than a 10 cent piece, situated about 2.5 cm. below the scar of the biopsy. The gross and microscopic appearance was that of cancer. She allowed me to perform a complete operation on November 27. During the course

of the operation no grossly involved glands were encountered, and sections from the base, middle and highest apex axillary glands showed no evidence of metastasis. However, sections from the breast showed cancer, although Dr. Gey was unable to grow it in vitro.

In view of the fact that this patient would not consent to a complete operation at first and did not consent to it for ten months, there was no choice other than delay. The fact that even after this delay of ten months, during which two courses of irradiation were given, no metastasis to the axillary glands was found, is evidence that the delay was not harmful. The patient was last heard from on Jan. 3, 1936, at which time she was well.

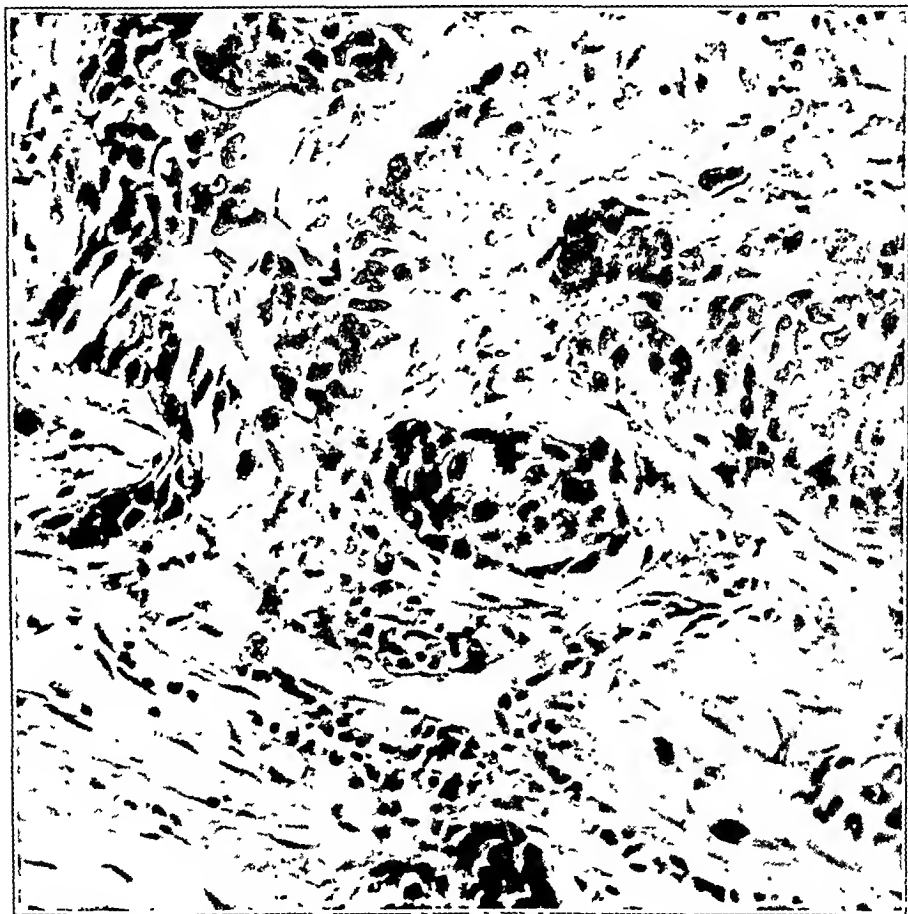


Fig. 24.—Photomicrograph showing residual cancer in the breast from a specimen removed at complete operation on Nov. 27, 1934, ten months after biopsy followed by two courses of preoperative irradiation.

One of the earliest and most interesting cases in this entire series is this last case, which presents an example of fully developed Paget's cancer of the nipple coming under observation before the stage of an ulcer.

Mrs. C., aged 46, came to the clinic on Dec. 11, 1934, because of a recurrent itching of the nipple of one year's duration and because a drop of blood had been observed recently. Examination showed an area of keratosis only 1 mm. in diameter, but there was a distinct difference in the appearance of the two nipples. The epidermis of the left nipple showed normal wrinkling, while on the right nipple the epidermis was tense, shiny and a little red, but there was no evidence of ulceration. No mass was palpable in the breast, and there were no palpable



Fig. 25.—Low power photomicrograph of a section through the nipple from tissue removed for biopsy on Dec. 12, 1934, showing fully developed Paget's carcinoma.

axillary glands. Even after repeated attempts I was unable to demonstrate any difference between the two breasts on transillumination, even directly beneath the nipple.

The day of the first examination, December 12, I excised the nipple, the areola and the central zone of the breast, using procaine hydrochloride. The frozen

section through the nipple showed a very early but fully developed Paget carcinoma, and on Jan. 7, 1935, Dr. Gey reported a growth of the tumor in tissue culture (figs. 25 and 26).

Dr. Curtis F. Burnam, at the Kelly Hospital, began roentgen irradiation to the axilla on December 12 and subsequently carried the irradiation over the supra-

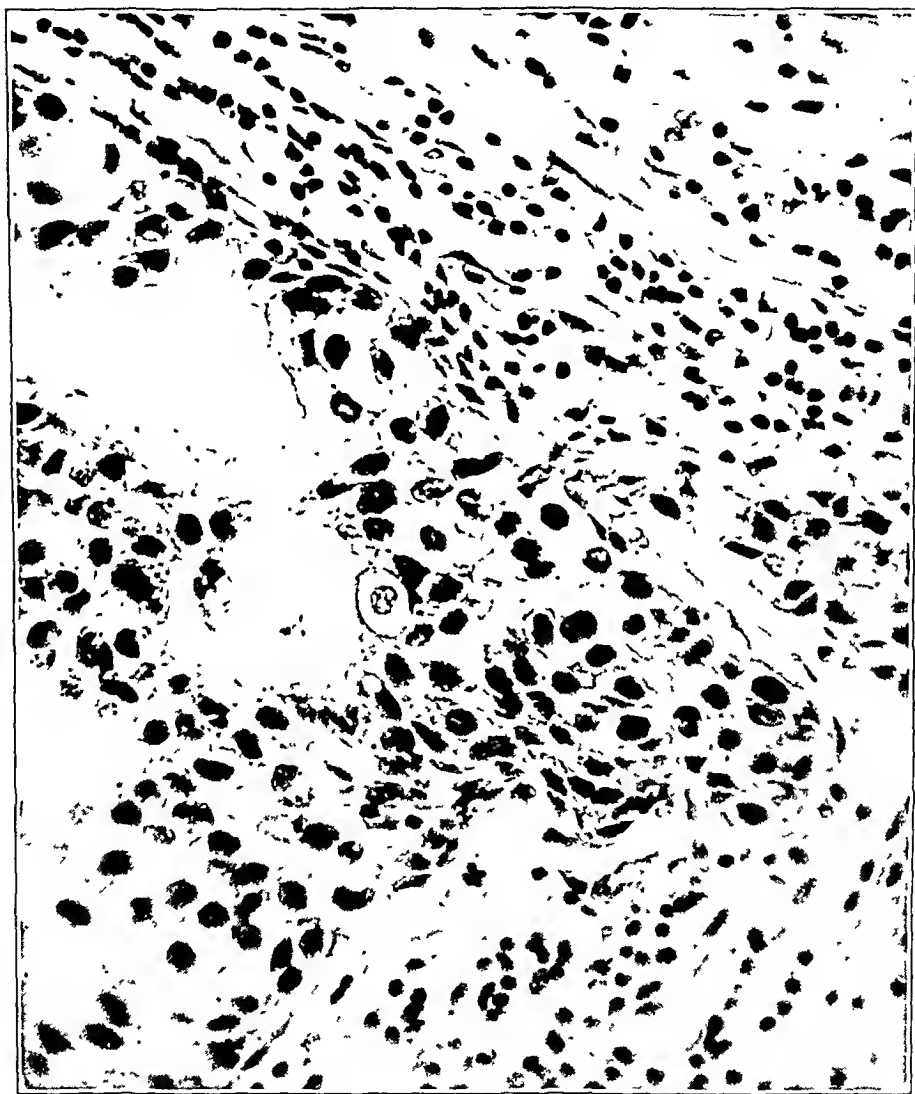


Fig. 26.—High power photomicrograph of an area of cancer beneath the nipple.

clavicular area and the breast. When the irradiation was complete the patient left for Florida, remaining until May. At the time of my examination, on May 16, 1935, there was no area in the breast suggesting recurrence, but there was a palpable gland the size of a 10 cent piece in the base of the axilla, although the following day I could not be quite certain about it.

Because there had been an interval of four months since the irradiation was completed, the patient was given a second course of irradiation from May 17, 1935, to June 15, 1935. On July 30, 1935, I performed a complete operation, and in the breast the only remaining evidence of cancer was a little nodule, the size of a pea, on the inner side of the scar. This nodule, however, had the gross appearance of cancer and was distinctly cancer histologically (fig. 27), but on August 13 Dr. Gey reported no growth in tissue culture. It will be recalled that this tumor grew *in vitro* before irradiation. There was no metastasis to the axillary glands. When the patient was last heard from, on March 15, 1936, there was no evidence of recurrence.

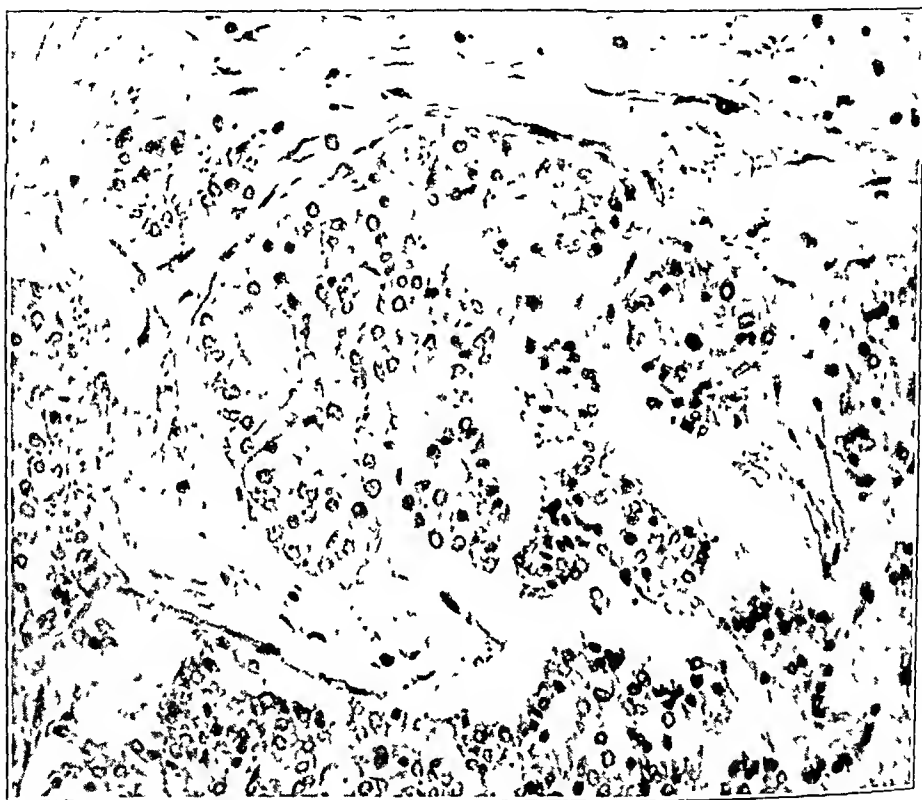


Fig. 27.—Low power photomicrograph of section taken through an area of residual cancer in the breast removed at complete operation on July 30, 1935, after two courses of preoperative irradiation.

In conclusion, I should like to refer particularly to two histologic pictures, that of the benign adenoma beneath the nipple and that of the very early stage of Paget's carcinoma of the nipple. (Compare figures 1 and 2 with figures 4, 5 and 6) In the former lesion the structure of the overlying epidermis is either normal or changed by pressure of the underlying tumor, so that it is thinned out, and the papillary bodies are either lost or not pronounced. Beneath the epidermis there is a narrow zone of fibrous stroma infiltrated by cells of the fibro-

blast and plasma cell type. Beneath this narrow band of stroma is this nonencapsulated tumor composed of irregular lobules which coalesce so intimately that the limitations of the separate lobules are almost indistinguishable, and the borders of these lobules when they can be identified are identified by the narrow zones of intralobular stroma separating them. The ducts and acini composing these lobules show diffuse dilatation and hypertrophy and hyperplasia of the mucous membrane lining with the formation of folds, and the cells themselves are of the columnar epithelial cell type, quite different from the cell characteristic of Paget's carcinoma. There are cystic and solid areas in the tumor, and sometimes stellate areas like those in basal cell carcinoma, and when these stellate basal cell areas are present the condition is more likely to be confused with carcinoma. It is important to note that in the benign adenoma beneath the nipple the basal cell layer of the epidermis is intact even though the papillary body may be flattened out.

In Paget's cancer, on the other hand, the first change is in the morphology of the spinal cells in the epidermis. The next change is the loss of the basal cell layer of the epidermis, and spinal cells are seen in contact with the stroma beneath. Paget's cancer of the nipple is a spinal cell carcinoma arising in the spinal cell layers of the epidermis, and in the earliest stages it can be recognized not only by the loss in the basal cell layer mentioned but by the tremendous enlargement in the size of the spinal cells taking part in the process and the marked changes in the morphology of these cells. Frequently these larger cells can be seen in the various stages of mitotic division and are so characteristic in appearance that they are sometimes given the name Paget cells, although Paget never described this disease histologically.

PEPTIC ULCERATION

THE RELATIVE PROTECTIVE VALUE OF THE ALKALINE DUODENAL JUICES

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NEW ORLEANS

Few subjects in medicine have received the perennial inquiry and the indomitable resoluteness of the clinical and experimental investigator that has the subject of peptic ulceration. This is evinced by the profound and voluminous literature amassed in the comparatively short period of approximately seventy-five years. This indubitable statement in itself is clearly indicative of the ineluctable conclusion that although much has been learned there is still little definitely known concerning the etiology of the disease. The multifarious hypotheses, the diversity of opinion and the eagerly challenged statements clearly reveal the perplexing problems of its causation.

No other condition has more provokingly incited the workers of the various special fields of medicine. The interest of the anatomist is aroused by the possible relationship of the blood and nerve supply to the characteristic location of the ulcer. The pathologist is attracted by its typical occurrence and its relationship to carcinoma. The presence of infection has instigated the bacteriologist to study the disease. The relationship of the digestive juices has actuated the physiologist toward its investigation. Its importance to the roentgenologist is manifest by its addition to his vainglorious list of accurately diagnosable conditions. The clinician is inspirited by the sad realization of the inadequacy of the purely medical measures as a complete cure. Finally, the surgeon is particularly interested, because he is always considered as the last resort and because he is offered an unusual opportunity to display his ingenuity in devising varied and more suitable operative procedures. These specialized interests and investigations undoubtedly have been to some extent conducive to the existing maze of confusion, bewilderment and contradiction. Each worker in his specialized field, viewing only his tessera in the mosaic, becomes prejudiced in his conception, allegorically recalling the six blind men and the elephant.

As a result, there are now no less than twelve theories and hypotheses, all of which emphasize certain factors which undoubtedly play

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some rôle in the etiology and pathogenesis of the disease. As these theories have been admirably reviewed in previous publications,¹ it will be superfluous as well as irrelevant to attempt their detailed discussion here. However, because of its appositeness in this particular investigation, it is considered pertinent as well as essential to give an account of the development of the chemical theory.

The chemical theory is the result of the accumulation of certain clinical and experimental observations. This strictly limited localization of the occurrence of ulcer with striking uniformity cannot be regarded as coincidental but must have a satisfactory explanation. The occurrence of ulceration in only those areas which are habitually bathed in acid chyme and in other parts of the intestinal tract only under exceptional circumstances which permit exposure to the gastric secretion has indicated the culpability of the acid gastric juice. On the basis of this reasoning, it has been concluded that there occurs insufficient neutralization or some abnormal inability of the alkaline duodenal juices to neutralize the normal or probably hyperacid gastric secretion. Investigators throughout the world have been stimulated to produce experimental evidence to substantiate this or to demonstrate some factor which might be totally absent, abnormally increased or abnormally diminished.

These studies have been directed in the main toward some method of approach by which the influence of the alkaline duodenal contents could be determined. A review of the diversified procedures and their modifications is a study in ingenuity, although the underlying principle remains the same. The purpose of the majority of the procedures has been to determine the relative values of the alkaline juices alone and in combination with each other. However, it was first necessary to devise some method by which ulcer could be produced in the dog, because it lends itself so well to experimental study and is particularly applicable to the study of ulceration, which so rarely occurs normally in this animal. That spontaneous chronic ulcer rarely occurs in the dog has been shown by Ivy² who did not find ulceration in eight hundred and fifty healthy

1. (a) Durante, L.: The Trophic Element in the Origin of Gastric Ulcer, *Surg., Gynec. & Obst.* **22**:399, 1916. (b) Greggio, Ettore: Des ulcères gastro-duodénaux, *Arch. de méd. exper. et d'anat. path.* **27**:533, 1916-1917. (c) Ivy, A. C.: Studies on Gastric and Duodenal Ulcer, *J. A. M. A.* **75**:1540 (Dec. 4) 1920. (d) Hurst, A. F.: Pathogenesis of Gastric and Duodenal Ulcer, *Guy's Hosp. Rep.* **74**:413, 1924. (e) Halperin, G.: The Pathogenesis of Gastro-Duodenal Ulcer, *Surg., Gynec. & Obst.* **43**:173, 1926. (f) Morton, Charles B.: Observations on Peptic Ulcer: I. A Method of Producing Chronic Gastric Ulcer; a Consideration of Etiology, *Ann. Surg.* **85**:207 and 879, 1927. (g) Held, I. W., and Goldbloom, A. A.: Pathogenesis of Peptic Ulcer, *M. Clin. North America* **14**:319, 1930. (h) Alvarez, Walter C.: Light from the Laboratory and the Clinic on the Causes of Peptic Ulcer, *Am. J. Surg.* **18**:207, 1932.

2. Ivy, A. C.: Studies on Experimental Gastric and Duodenal Ulcer, *Am. J. Physiol.* **49**:143, 1919.

and diseased dogs at autopsy. Subsequently at autopsy on nine hundred dogs, only one chronic and one acute ulcer were found, each occurring in an animal that was diseased and cachectic.³ In two hundred apparently normal cats and dogs, Mann⁴ found no gastric lesion. Turck's⁵ experience was also the same in examinations of one hundred and eighty-nine healthy and eighty-two diseased dogs. There is no satisfactory explanation of this apparent immunity to peptic ulceration possessed by the lower animals.

In addition to the difficulty of consistently producing ulcer experimentally, the early investigators were faced with the difficulty of producing chronic ulcer. It was relatively simple to produce acute ulcer, but it was not until 1923, when Mann and Williamson⁶ published their method, that a technic was devised by which chronic ulcer could be produced with consistency. Previous to this there were reported only a few cases of characteristic punched-out or perforating ulcer.

In 1903 Watts,⁷ with Sowers, performed anterior gastrojejunostomies on dogs. One dog died three months after the operation, and necropsy revealed a perforating jejunal ulcer opposite the stoma, with resulting peritonitis. Watts attributed this to the hyperacid gastric juice emptying directly into the jejunum. Montgomery⁸ in 1923 studied the effect of hematoma and different types of suture material in anterior and posterior gastro-enterostomies in ten groups of experiments. He found only four ulcers in sixty dogs studied. Dott and Lim⁹ had a somewhat similar experience. Borzkey,¹⁰ Exalto¹¹ and von Roojen¹² observed jejunal ulcer after gastro-enterostomy, and the operation in man was

3. Ivy, A. C.: Contributions to the Physiology of the Stomach, *Arch. Int. Med.* **25**:6 (Jan.) 1920.

4. Mann, Frank C.: A Study of the Gastric Ulcers Following Removal of the Adrenals, *J. Exper. Med.* **23**:203, 1916.

5. Turck, Fenton B.: Ulcer of the Stomach: Pathogenesis and Pathology, *J. A. M. A.* **46**:1753 (June 9) 1906.

6. Mann, F. C., and Williamson, C. S.: The Experimental Production of Peptic Ulcer, *Ann. Surg.* **77**:409, 1923.

7. Watts, S. H.: A Case of Peptic Ulcer in the Jejunum of a Dog Following Gastro-Enterostomy, with Review of the Cases Reported in Man, *Bull. Johns Hopkins Hosp.* **14**:191, 1903.

8. Montgomery, A. H.: Gastrojejunal Ulcer: An Experimental Study, *Arch. Surg.* **6**:136 (Jan.) 1923.

9. Dott, D. M., and Lim, R. K. S.: Experimental Jejunal Ulcer, *Quart. J. Exper. Physiol. (supp.)* **11**:109, 1923.

10. Borzkey, K.: Die chirurgische Behandlung des peptischen Magen- und Duodenalgeschwürs und seiner Komplikationen und die damit erreichten Ergebnisse, *Beitr. z. klin. Chir.* **57**:56, 1908.

11. Exalto, J.: Ulcus jejuni nach Gastroenterostomie, *Mitt. a. d. Grenzgeb. d. Med. u. Chir.* **23**:13, 1911.

12. von Roojen, quoted by Alvarez.^{1h}

soon considered dangerous. Many other chance observations have been reported by the early investigators, but their detailed review would be superfluous here. More pertinent is the consideration of the production of ulcer in the study of the deviation of the alkaline duodenal juices. These will be discussed in combination and separately.

Probably the earliest recognition of the importance of the bile and pancreatic juices in preventing the formation of ulcer is that of Bickel,¹³ who in 1909 made a rather interesting chance observation. In two dogs he performed duodenectomy after closure of the pylorus and gastro-enterostomy to reestablish the continuity of the gastro-intestinal tract. The common bile and pancreatic ducts were sutured to the skin of the abdomen. One month later one dog died of perforation, with resulting peritonitis of one of several jejunal ulcers just distal to the stoma. Five years later Langenskiöld,¹⁴ with the full realization of the importance of this work, published the results of his experiments, which eventually led to the more consistent procedure of Mann and Williamson.⁶ He severed the duodenum just proximal to the opening of the bile duct and closed the distal ends. He then severed the jejunum several centimeters distal to the duodenum and anastomosed the distal end (end to end) to the proximal end of the duodenum and joined the proximal end of the jejunum to a loop of jejunum further caudad (end to side). In this manner the bile and pancreatic juices were shunted into the lower part of the small intestine. Because the animal appeared ill, it was killed, and an ulcer was found in the short segment of the duodenum between the stomach and the jejunum. This same procedure was repeated by McCann¹⁵ in 1929, except that the proximal end of the severed jejunum was anastomosed to the terminal portion of the ileum (end to side), but ulcers developed in the jejunum rather than in the duodenum. By slightly modifying Langenskiöld's operation, Mann and Williamson⁶ in 1923 proposed their "surgical duodenal drainage" procedure by which typical chronic ulcer could be produced consistently. Their operation consisted essentially in isolating the duodenum by severing it from the pylorus and the jejunum, closing its oral end and anastomosing its distal end to the terminal portion of the ileum from 25 to 75 cm. from the ileocecal junction and then anastomosing the proximal end of the jejunum to the pylorus. Fourteen of sixteen animals coming to necropsy showed typical subacute or chronic ulcer.

13. Bickel, A.: Beobachtungen an Hunden mit extirpiertem Duodenum, Berl. klin. Wchnschr. **46**:1201, 1909.

14. Langenskiöld, F.: Ueber die Widerstandsfähigkeit einiger lebender Gewebe gegen die Einwirkung eiweisspaltender Enzyme, Skandinav. Arch. f. Physiol. **31**: 1, 1913.

15. McCann, James C.: Experimental Peptic Ulcer, Arch. Surg. **19**:600 (Oct.) 1929.

Mann contended that there are two important factors in the causation and prevention of healing of such an ulcer, viz., a chemical and a mechanical factor. He stated that although the former has been recognized, the latter has not been sufficiently appreciated, and he emphasized the fact that the ulcer develops at the site where the mucosa was subjected to the greatest force of impingement of the gastric chyme as it was propelled from the stomach in a nozzle-like manner. To emphasize this propulsive action further, Mann¹⁶ performed the "surgical duodenal drainage" operation and then produced a typical hour-glass stomach in the prepyloric region, so that the stomach was divided into two pouches, communicating at the lesser curvature through a small opening. In this manner the propulsive power of the stomach was considerably lessened, and the animals were remarkably resistant to the development of ulcer. McCann¹⁷ further stressed the importance of this mechanical factor by such suggestive evidence as the demonstration in one ulcer specimen of fifty or more hairs of the dog embedded in the sloping wall of the distal half of the crater. He surmised that the gastric chyme was thrown against this segment with sufficient force to embed the hairs in the wall of the ulcer.

The ulcers produced by the method of Mann and Williamson usually developed in from three to four weeks after operation and generally occurred on the posterior wall of the jejunum slightly to the right of the axial line and rarely involved the suture line. Usually there was only one ulcer, but occasionally there was a "kissing ulcer" and rarely a third ulcer. The occurrence of this third distal ulcer is explained by Mann rather fancifully as due to "a splash of the contents from the area of the first ulcer." These ulcers resembled in every way the ulcers found in man, being more or less circular and punched out, with overhanging edges; they always involved the entire thickness of the mucosa and usually penetrated the intestinal wall to a considerable depth.

The results obtained by the "surgical duodenal drainage" operation of Mann and Williamson have been corroborated by many others. Similar experiments were performed by Morton¹⁸ on twenty dogs, and typical subacute chronic ulcer developed in all. Gallagher and Palmer¹⁹ observed jejunal ulcer in thirty-eight of forty-seven animals on which

16. Mann, F. C.: The Chemical and Mechanical Factors in Experimentally Produced Peptic Ulcer, *S. Clin. North America* 5:753, 1925.

17. McCann, J. C.: Further Studies in Experimental Peptic Ulcer: Chemistry of Experimental Ulcer, *Proc. Staff Meet., Mayo Clin.* 2:284, 1927.

18. Morton, C. B.: Observations on Peptic Ulcer: V. Findings in Experimentally Produced Peptic Ulcer; Etiology and Therapeutic Consideration, *Ann. Surg.* 87:401, 1928.

19. Gallagher, W. J., and Palmer, W. L.: Experimental Jejunal Ulcer: Relative Importance of Mechanical and Chemical Factors, *Proc. Soc. Exper. Biol. & Med.* 30:468, 1932.

the "duodenal drainage operation" was performed (an incidence of 70.2 per cent). They also noted that there was no relationship between the site of the duodenal secretion, whether high or low in the intestine, and the rapidity of the formation of the ulcer. A similar incidence was reported by Weiss and Gurriaran²⁰ in fifteen dogs. Neumann, de Moor and Deloyers²¹ also noted a high incidence of ulcer after this operation. Jenkins and Palmer²² attempted to minimize the importance of the mechanical factor so strongly emphasized by Mann and to strengthen the influence of the chemical factor. They performed the operation of Mann and Williamson, with the exception that the gastro-enterostomy stoma was modified by a side to side anastomosis, and ulcer developed in 90 per cent of the animals. They contended that they obtained just as high an incidence of ulcer when there was no mechanical injury due to the injection of chyme from a narrow stoma and strongly emphasized the importance of the chemical action of unneutralized gastric juice on the jejunal mucosa. This was verified by Matthews and Dragstedt,²³ who obtained ulcer in all of five dogs in which a large anastomosis was made between the stomach and the jejunum.

Morton¹⁸ performed the operation of Mann and Williamson and produced typical chronic peptic ulcer in 50 per cent of the animals in which he had previously denuded mucosal areas on the lesser and the greater curvature. Delay in healing was much more marked on the lesser than on the greater curvature. Besides these lesions of the stomach, ulceration developed at the usual site in the jejunum in practically all animals. Even after a modified form of duodenal drainage in which the pyloric third of the stomach was resected so as to diminish the acid-secreting area of the stomach, ulcer usually developed in the jejunum. From an analysis of these and subsequent experiments, Morton²⁴ was inclined to favor the mechanical factor. He expressed the belief that the chronicity is probably due to a relative imbalance between the acids of the stomach and the alkaline juices of the duodenum,

20. Weiss, A. G., and Gurriaran, G.: *Ulcères chroniques expérimentaux erées par la dérivation des sucs alcalins duodénaux*, *Arch. d. mal. de l'app. digestif* **20**: 63, 1930.

21. Neumann, F.; de Moor, P., and Deloyers, L.: *Contribution à l'étude de la pathogénie des ulcères gastroduodénaux: Dérivation totale des sucs duodénaux, biliaires, et pancréatiques dans la l'iléon terminal*, *Compt. rend. Soc. de biol.* **105**: 887, 1930.

22. Jenkins, H. P., and Palmer, W. L.: *Studies on Experimental Jejunal Ulcers*, *Proc. Soc. Exper. Biol. & Med.* **28**:935, 1931.

23. Matthews, W. B., and Dragstedt, L. R.: *The Etiology of Gastric and Duodenal Ulcer*, *Surg., Gynec. & Obst.* **55**:265, 1932.

24. Morton, C. B.: *Observations on Peptic Ulcer: VI. Preliminary Report of Clinical Experiments with Gastroduodenal Analysis*, *Am. J. M. Sc.* **177**:65, 1929.

causing incomplete or faulty neutralization of the acid gastric chyme. He²⁵ also stressed the possibility of an improper function of the pylorus.

Neumann, Deloyers and de Moor²⁶ obtained ulcers in 50 per cent of ten "surgical duodenal drainage" operations. Beaver and Mann²⁷ performed this same operation with the addition of preliminary sectioning of the vagus nerve in one group of animals and the splanchnic nerve in another. Ulceration developed in all except one in which vagotomy had been done. They concluded that sectioning of the gastric nerve did not prevent the formation of ulcer in that portion of the intestine receiving the gastric contents after removal of the alkaline secretions.

Owings and Smith²⁸ modified the procedure of Mann and Williamson by performing side to side anastomosis of the jejunum and stomach in twenty-six animals. Typical chronic ulcer developed in ten of the dogs. They then reconducted the duodenal secretion over the ulcerated areas in subsequent operations and obtained complete healing in four and partial healing in two of the animals. Similar healing was obtained by Morton,¹⁸ who performed the "duodenal drainage operation," and at subsequent laparotomy, when an ulcer was found at the usual site in the jejunum, he performed gastro-enterostomy. From four to sixteen days after the latter procedure unmistakable signs of healing were found. Mann²⁹ also obtained healing by gastro-enterostomy after previously producing an ulcer by the "duodenal drainage" operation.

Thus it has been irrefutably established that deviation of all the alkaline duodenal juices will inevitably result in the formation of an ulcer. Mann attempted to explain this occurrence by the chemical and mechanical factors. It has been shown, however, that in spite of minimizing the latter, ulceration will develop in a high percentage of animals. However, the chemical factor cannot be abnegated so easily, as it is a much more tangible factor. The exact nature of the disturbed relationship between the acid gastric juice and the alkaline duodenal juices has not been satisfactorily explained.

25. Morton, C. B.: Peptic Ulcer: IX. Chronic Lesions of the Duodenum Following Experimentally Produced Pyloric Dysfunction, *Arch. Surg.* **28**:467 (March) 1934.

26. Neumann, F.; Deloyers, L., and de Moor, P.: Contribution à l'étude de la pathogénie des ulcères duodénaux, *Bull. Acad. roy. de méd. de Belgique* **12**: 477, 1932.

27. Beaver, M. S., and Mann, F. C.: The Production of Peptic Ulcer After Section of the Gastric Nerve, *Ann. Surg.* **94**:1116, 1931.

28. Owings, J. C., and Smith, I. H.: Experimental Production and Cure of Jejunal Ulcers, *Proc. Soc. Exper. Biol. & Med.* **29**:832, 1932.

29. Mann, F. C.: Production and Healing of Peptic Ulcer: An Experimental Study, *Minnesota Med.* **8**:638, 1925.

Boldyreff³⁰ maintained that the acidity of the gastric juice is regulated by the regurgitation of the duodenal alkali into the stomach. If this theory is accepted, these procedures would effect a persistent state of high gastric acidity, which might account for the production of ulcer. On the other hand, it is possible that the gastric acidity is independent of the regurgitation of the duodenal alkalis and that the ulcer is produced by the acid peptic acidity of the normal gastric chyme, which remains unbuffered or undiluted beyond the pylorus after deviation of the duodenal secretion. In order to determine which of these hypotheses is the more probable, experiments have been devised which produce a reflux of the duodenal secretions into the stomach.

Keppich³¹ in 1921 performed experiments somewhat similar to those devised by Chlumsky³² and Schmilinsky,³³ in which the proximal end of the upper part of the jejunum was anastomosed to the fundus of the stomach and the distal end to the pylorus (end to end) after the distal end of the duodenum was closed. In this manner the pancreatic, biliary and duodenal secretions must pass through the stomach to the jejunum. No ulcers formed after this procedure. On the other hand, McCann¹⁵ repeated this procedure, except that he severed the duodenum at the pyloric sphincter, and obtained jejunal ulcer in 80 per cent of twenty-six dogs. The curious fact, shown by McCann, that there was no appreciable modification in the gastric acidity curve after this procedure may be elucidative. McCann's procedure was slightly modified by Weiss, Graves and Gurriaran,³⁴ so that instead of deviating duodenal secretion to the fundus it was deviated to the prepyloric region. Ulceration did not develop in any of fourteen dogs operated on. Graves,³⁵ working in the surgical experimental laboratory at Tulane University, performed similar experiments on eleven dogs with the same result and suggested that the acid gastric chyme was sufficiently mixed with the alkaline duodenal secretion to render it noninjurious to the jejunal mucosa. He also concurred with Weiss and his co-workers that trauma

30. Boldyreff, W.: The Self-Regulation of Acidity of the Gastric Contents and the Real Acidity of the Gastric Juice, *Quart. J. Exper. Med.* **8**:1, 1915.

31. Keppich, J.: Ueber das Ulcus pepticum jejuni nach Pylorusausschaltung, *Zentralbl. f. Chir.* **48**:118, 1921.

32. Chlumsky, V.: Ueber die Gastroenterostomie, *Beitr. z. klin. Chir.* **20**:231 and 487, 1898; Weitere Erfahrungen über die Gastroenterostomie, *ibid.* **27**:1 and 282, 1900.

33. Schmilinsky, H.: Die Einleitung der gesamten Duodenalsäfte in den Magen (innere Apotheke), *Zentralbl. f. Chir.* **45**:416, 1918.

34. Weiss, A. G.; Graves, A., and Gurriaran, G.: La dérivation intragastrique des sucs alcalins duodénaux, *Compt. rend. Soc. de biol.* **109**:916, 1932.

35. Graves, Amos M.: Combined and Separate Effects of Bile, Pancreatic Secretion, and Trauma in Experimental Peptic Ulcer, *Arch. Surg.* **30**:833 (May) 1935.

is of little or no importance. Ivy and Fauley³⁶ similarly rarely found ulceration after this operation. In contrast to these results, Fontaine and Kunlin³⁷ obtained ulcer complicated by profuse hemorrhage and perforation under similar circumstances and concluded that Boldyreff's reflex is of no consequence. Thus exists the maze of confusion and contradiction and the resulting difficulty obfuscating any effort to draw conclusions. About all that it is safe to assume is the undeniable fact that jejunal ulcer will usually develop if duodenal secretions are deviated. Which of these secretions, if any, plays a feature rôle? Is it the succus entericus, the pancreatic or the biliary juices? A variety of methods have been devised to determine this. Almost all have the underlying principle of exclusion of one or more of the juices. By excluding these juices either separately or in combination it has been possible to determine indirectly their protective influence against the formation of a peptic ulcer.

THE EFFECT OF THE COMBINED DEVIATION OF BILE AND PANCREATIC JUICES

Kehrer³⁸ in 1914 ligated the common duct and performed cholecystenterostomy and transplantation of the pancreatic duct into the terminal portion of the ileum. Of fifteen dogs operated on, multiple erosions and ulcers developed in the stomach in six, and one of these presented ulcers in the duodenum. Mann and Williamson⁶ transplanted bile and pancreatic ducts into the terminal portion of the ileum in thirty-one dogs and noted ulcer in ten (33 per cent). This procedure left only the succus entericus to protect the duodenal mucosa. Graves³⁵ found peptic ulcer in the duodenum after performing duodenectomy in two stages, the first stage consisting of ligation of the common duct and cholecystenterostomy and transplantation of pancreatic duct into the jejunum and the second stage consisting of resection of the duodenum and gastrojejunostomy. Two of the four dogs operated on died after the first stage with perforating peptic ulcer and peritonitis. On the other hand, Owings and Smith³⁹ did not obtain ulceration after per-

36. Ivy, A. C., and Fauley, G. B.: Factors Concerned in Determining the Chronicity of Ulcers in the Stomach and Upper Intestine, *Am. J. Surg.* **11**:531, 1931.

37. Fontaine, R., and Kunlin, J.: Le reflex duodénal intervient-il dans la production des ulcères peptiques expérimentaux? *Presse méd.* **40**:1752, 1932; Ulcères peptiques expérimentaux obtenus par la dérivation des sucs intestinaux avec intégrité du pylore, *Compt. rend. Soc. de biol.* **110**:294, 1932.

38. Kehrer, J. K. W.: Ueber die Ursache des runden Magengeschwüres, *Mitt. a. d. Grenzgeb. d. Med. u. Chir.* **27**:679, 1914.

39. Owings, J. C., and Smith, I. H.: The Etiology of Duodenal Ulcers, *Proc. Soc. Exper. Biol. & Med.* **29**:833, 1932.

forming similar operations. Of more than passing interest in this regard is the case reported by Morton and Graham,⁴⁰ in which a badly diseased gallbladder was excised, five stones were removed from the common duct and choledochostomy was performed. After removal of the tube and on the twelfth day after operation, complete obstruction occurred, acute symptoms of ulcer developed, and the patient died of an acute hemorrhage from a large duodenal ulcer, which was discovered at necropsy. They attributed the formation of the ulcer to interference with the discharge of alkaline pancreatic juice and bile into the duodenum by the biliary calculus. Bauer and Aron⁴¹ resected the pancreas and left only a small amount for internal secretion, and two months later they ligated the common duct and anastomosed the gallbladder to the terminal portion of the ileum. No ulceration developed. Two and a half months later they resected the duodenum, and an ulcer developed in the jejunum distal to the gastrojejunostomy. They concluded that the duodenal secretion is most important in the protection against the formation of ulcer. Thus it is seen that the deviation of the combined bile and pancreatic secretions will result in a comparatively high incidence of ulcer; in other words, the duodenal secretion alone is not altogether sufficient protection against the formation of ulcer.

EFFECT OF THE ELIMINATION OF THE DUODENAL SECRETION ALONE

Mann and Williamson⁶ performed duodenectomy and made the jejunum with the transplanted bile and pancreatic ducts occupy the place of the duodenum. Of ten dogs operated on, ulcer developed in two, three hundred and ninety-three days and five hundred and fifteen days after operation, respectively. Similar duodenectomy was performed by Mann and Kawamura⁴² in the dog, cat, hog, goat and monkey, and careful observations were made for over two and a half years after operation. They concluded that the duodenum is of little, if any, importance in the life of these animals. Grey,⁴³ after similar experiments, came to the same conclusion. Weiss and Gurriaran²⁹ noted no difference in gastric acidity before and after operation. Graves³⁵ performed

40. Morton, C. B., and Graham, J. B.: Observations on Peptic Ulcer: VII. Clinical Corroboration of Experimental Data, *Ann. Surg.* **91**:73, 1930.

41. Bauer, R., and Aron, E.: Rôle respectif de la suppression des sécrétions pancréatique et biliaire, et de la résection duodénale dans la production des ulcères peptiques expérimentaux, *Compt. rend. Soc. de biol.* **113**:1063, 1933.

42. Mann, F. C., and Kawamura, K.: An Experimental Study of the Effects of Duodenectomy, *J. A. M. A.* **73**:878 (Sept. 20) 1919; Duodenectomy (An Experimental Study), *Ann. Surg.* **75**:208, 1922.

43. Grey, E. G.: Duodenectomy—Its Effect upon the Life of an Animal Transplantation of the Pancreatic Duct, *Surg., Gynec. & Obst.* **28**:36, 1919.

duodenectomy in three stages, and one animal lived eight and a half months after the last stage. This, in his opinion, offered indisputable evidence that the duodenum is not essential to life. Mann and Bollman,⁴⁴ on the other hand, concluded that duodenal mucosa and secretions are probably the most important factors in the prevention of the formation of peptic ulcer, with pancreatic juice next and bile of least importance.

THE EFFECT OF DEVIATION OF THE PANCREATIC JUICE

The importance of the combined bile and duodenal juices has been studied by eliminating the pancreatic juice either by total pancreatectomy, by ligation or transplantation of the pancreatic duct or by the production of a fistula in the pancreatic duct. With the exception of transplantation of the duct, all the procedures are open to serious objections, as the normal function is too greatly altered. Steinberg⁴⁵ performed total pancreatectomy in dogs with a Pavlov pouch and observed prolonged periods of active gastric secretion, a great increase in the concentrations of pepsin, longer periods of gastric retention and constant retching and vomiting. Whereas the chlorides of the gastric juice were uniform, the gastric juice was low in acid and high in pepsin during the continuous secretion. Postmortem examination revealed severe gastritis with a highly hemorrhagic mucosa. Similarly, Fauley and Ivy⁴⁶ had somewhat the same experience, although they also ligated the duct. Departing somewhat from the usual procedures, Grey⁴⁷ attempted to ascertain how the stomach would react to a more or less continuous influx of relatively strong alkaline fluid. This was provided for by transplanting the large pancreatic duct into the wall of the stomach of seven dogs after the lesser duct was ligated and divided. Grey observed only a moderate decrease in the acidity level of ingestion in later stages of digestion. Jona⁴⁸ made the general statement that ligation of the main pancreatic duct will result in ulceration of the duodenum and jejunum, but he did not give the number of dogs operated on or the incidence of ulcer. Berg⁴⁹ made observations on sixteen dogs deprived completely of pan-

44. Mann, F. C., and Bollman, J. L.: Experimentally Produced Peptic Ulcer: Development and Treatment, *J. A. M. A.* **99**:1576 (Nov. 5) 1932.

45. Steinberg, M. E.: The Gastric Juice in Pancreatic Diabetes, *Am. J. Physiol.* **56**:371, 1921.

46. Fauley, G. B., and Ivy, A. C.: The Effect of Exclusion of Pancreatic Juice on Gastric Digestion, *Am. J. Physiol.* **89**:428, 1929.

47. Grey, E. G.: The Diversion of the Pancreatic Juice from the Duodenum into the Stomach: Its Effects upon the Level of Gastric Acidity and upon the Pancreas, *J. Exper. Med.* **26**:825, 1917.

48. Jona, J. L.: A Further Contribution to the Experimental Study of Duodenal Ulcer, *M. J. Australia* **1**:316, 1919.

49. Berg, Benjamin N.: Peptic Ulcers: Comparative Frequency After Deprivation of Bile and Pancreatic Juice, *Arch. Surg.* **28**:1057 (June) 1934.

creatic juice by means of fistulas made according to the technic of Rous and McMaster,⁵⁰ as adapted by Elman and McCaughan.⁵¹ Daily rations of food were supplemented by sodium chloride administered intravenously in physiologic solution. All of the animals lost weight progressively and showed evidence of profound metabolic disturbances. Necropsy revealed definite and marked degenerative changes in the liver, and peptic ulcer was found in only one animal, which was one of the three in which jaundice developed. This, according to Berg, indicated that the absence or neutralization of gastric acidity by pancreatic juice is not an important factor. Another publication by Berg and Zucker,⁵² dealing with similar experiments, reported the same results. Berg and Jobling⁵³ noted no lesions in a series of nine dogs with pancreatic fistulas. Graves³⁵ found no ulceration in a series of twelve dogs in which the pancreatic duct was transplanted into the distal end of the jejunum. Of this group, six were subjected to a second stage operation in which the duodenal secretions and bile were drained into the ileum, and the jejunum with its pancreatic duct was anastomosed to the stomach. Five dogs died of ulcer, complicated with perforation in three and with hemorrhage in two. Loewy⁵⁴ anastomosed the pancreatic duct to the right ureter in four dogs and produced a pancreatic fistula in one dog. He observed no ulceration in any of the five dogs and concluded that the absence of pancreatic juice in the duodenum is not responsible for the formation of ulcer. A similar observation was made by Owings and Smith,³⁹ who transplanted the pancreatic duct into the jejunum 18 inches (45 cm.) below the ligament of Treitz in one group of animals. Neumann, Deloyers and de Moor⁵⁵ also observed no ulceration in six dogs in which the main pancreatic duct was ligated and the accessory pancreatic duct transplanted into the terminal portion of the ileum. In a subsequent publication²⁶ they reported the absence of ulceration in a series of eight dogs operated on in the same manner.

50. Rous, P., and McMaster, P. D.: A Method for the Permanent Sterile Drainage of Intra-Abdominal Ducts as Applied to the Common Duct, *J. Exper. Med.* **37**:11, 1923.

51. Elman, Robert, and McCaughan, John M.: On the Collection of the Entire External Secretion of the Pancreas Under Sterile Conditions and the Fatal Effect of Total Loss of Pancreatic Juice, *J. Exper. Med.* **45**:561, 1927.

52. Berg, B. N., and Zucker, T. F.: Liver Changes After Deprivation of External Pancreatic Secretion, *Proc. Soc. Exper. Biol. & Med.* **29**:68, 1931; Comparative Frequency of Peptic Ulcers After Deprivation of Bile and Pancreatic Juice, *ibid.* **30**:330, 1932.

53. Berg, B. N., and Jobling, J. W.: Biliary and Hepatic Factors in Peptic Ulcer, *Arch. Surg.* **20**:997 (June) 1930.

54. Loewy, G.: Influence de la dérivation du suc pancréatique sur la production des ulcères duodénaux, *Compt. rend. Soc. de biol.* **111**:783, 1932.

55. Neumann, F.; Deloyers, L., and de Moor, P.: Les ulcères duodénaux, *Arch. d. mal. de l'app. digestif* **21**:511, 1931.

Zucker, Newburger and Berg,⁵⁶ in studying the inorganic constituents of blood and urine in dogs with pancreatic fistula, made no mention of the formation of ulcer in observations on twenty animals. In contrast to the foregoing findings, Elman and Hartmann⁵⁷ found duodenal ulcer in each of six dogs in which there was a continued loss of pancreatic juice. These dogs were kept alive for about thirteen days with the intraperitoneal administration of Ringer's solution. As a result of a 100 per cent incidence of ulcer, they felt justified in assuming that the presence of pancreatic juice in some way protects the duodenum against the formation of ulcer and that bile plays a minor rôle as compared to pancreatic juice. Matthews and Dragstedt²³ also observed chronic duodenal ulcer in dogs with a fistula in the pancreatic duct and stated that their formation could be prevented by the oral administration of *calcium carbonate or finely ground meal*. Hoerner⁵⁸ reported a curious but interesting observation. After evulsion of the pancreatic duct no lesion was found in the gastric or duodenal mucosa, but when a fistula of the pancreatic duct was established, peptic ulcer developed in 42 per cent of the animals. In the dogs in which ulcer developed, a check of previous determinations revealed an increase in the amount of gastric secretion and acidity, which was in definite contrast to the results obtained in the other animals of the series in which no lesion developed.

THE EFFECT OF THE BILIARY SECRETION ALONE

The influence and the effect of the biliary secretions have been studied by methods similar to those used in the study of the pancreatic juice. Kapsinow⁵⁹ in 1926 was one of the first investigators to observe the effect of bile excluded from the duodenum by cholecystnephrostomy. In this manner he overcame the objection of possible ascending infection of the biliary tract, intestinal trauma and the possibility of any bile finding its way into the intestine. He performed the operation in two stages: (1) cholecystnephrostomy and, at a later date, when healing was complete, (2) ligation and division of the common bile duct. Of forty-three animals operated on, typical duodenal ulcer developed in seventeen (39.5 per cent). In two instances there was definite perfora-

56. Zucker, T. F.; Newburger, M. S., and Berg, B. N.: Inorganic Constituents of Blood and Urine in Dogs with Pancreatic Fistula, *Proc. Soc. Exper. Biol. & Med.* **27**:666, 1930.

57. Elman, R., and Hartmann, A. F.: Spontaneous Peptic Ulcers of Duodenum After Continued Loss of Total Pancreatic Juice, *Arch. Surg.* **23**:1030 (Dec.) 1931.

58. Hoerner, M. T.: The Effect of Exclusion of the Pancreatic Juice from the Duodenum: An Experimental Study, *Proc. Staff Meet., Mayo Clin.* **9**:473. 1934.

59. Kapsinow, R.: The Experimental Production of Duodenal Ulcer by Exclusion of Bile from the Intestines, *Ann. Surg.* **83**:614, 1926.

tion. Neumann, Deloyers and de Moor⁵⁵ performed cholecystenterostomy near the terminal portion of the ileum after ligating the common duct and obtained chronic duodenal ulcer in five of seven dogs operated on (70 per cent). The dogs remained in excellent health until ulceration developed, and the gastric acidity did not change appreciably before or after operation. The authors performed this same operation again on two other series, one of seven⁶⁰ and another of eight dogs,²⁶ and obtained ulceration in 57 and 62.5 per cent, respectively. Weiss and Gurriaran²⁰ performed the same operation on a series of three dogs, in one of which an ulcer developed. A similar operation was performed by Owings and Smith,³⁹ except that the cholecystenterostomy was performed at a higher level, about 18 inches below the ligament of Treitz. Acute duodenal ulcer developed in two of five dogs. Similarly Graves,³⁵ in a series of eight dogs, obtained one completely healed duodenal ulcer, which produced stenosis.

The protective influence of bile was rather convincingly demonstrated by Ochsner, Gage and Hosoi⁶¹ while working in the experimental surgical laboratory at Tulane University. They performed a gastric pouch of the Heidenhain type from the greater curvature and of the Pavlov type from the lesser curvature plus anastomosis of the proximal portion of the jejunum to the pouch. They obtained ulcer in 100 per cent of the animals on which the former procedure was done and in 71 per cent in which the latter was done, or an average of 85 per cent. In another series in which the procedure was similar to the foregoing, but with the addition of anastomosis of the fundus of the gallbladder to the pouch, the incidence of ulcer was reduced from 100 to 28 per cent in the dogs with a pouch in the greater curvature and from 71 to 50 per cent in the animals with a pouch in the lesser curvature, or from an average of 85 per cent in the former series to 39 per cent in the latter group.

Exclusion of bile by the fistula method has also been a popular procedure for determining its effect. Rous and McMaster⁵⁰ described an excellent method for the permanent sterile drainage of a common bile duct. They used this method on seventeen dogs over a period ranging up to three months and observed that the animals remained in good health throughout except for some anemia. They made no mention of ulcer occurring. Berg, Johnston and Jobling,⁶² using this same method for the production of an external biliary fistula in a series of nine dogs

60. Neumann, F.; de Moor, P., and Deloyers, L.: Contribution à l'étude de la pathogénie des ulcères gastro-duodénaux. Dérivation exclusive de la bile dans l'iléon terminal, *Compt. rend. Soc. de biol.* **105**:890, 1930.

61. Ochsner, A.; Gage, M., and Hosoi, K.: The Relationship of Peptic Ulceration to Gastric Chemism, *Proc. Soc. Exper. Biol. & Med.* **31**:1260, 1934.

62. Berg, B. N.; Johnston, A., and Jobling, J. W.: Duodenal and Gastric Ulcers in Dogs with Biliary Fistulas, *Proc. Soc. Exper. Biol. & Med.* **25**:334, 1928.

living from twelve to forty-six days, observed duodenal ulcers in seven animals, an incidence of 77.7 per cent. They also noted that all the dogs lost an average of 25 per cent in weight. Two years later Berg and Jobling⁵³ reported the results in another series of twenty-three dogs on which a similar procedure had been performed, but in which there was an uninterrupted flow of bile, an intermittent flow of bile or complete biliary obstruction. In thirteen of the twenty-three dogs a duodenal or gastric lesion developed, an incidence of 56.5 per cent. Because of the observation that under poor environmental conditions and poor preparation of food, ulceration developed in 100 per cent of their animals, whereas under improved conditions the incidence diminished to 13 per cent, the authors suggested that the formation of ulcer was in some way related to the environment. They also opined that probably one of the effects of the exclusion of bile may be the disturbance of the regulatory mechanism of the secretion of mucus, which exposes the surface of the epithelium to the action of the gastric juice.

Another method of studying the influence of bile in the formation of peptic ulcer is by excluding the duodenal and pancreatic secretions. Graves⁵⁵ accomplished this by transplanting the common bile duct into the jejunum as the first stage and at a subsequent date (average thirty days) performing "surgical duodenal drainage" and substituting the jejunum with its common duct transplant. Of six dogs operated on, one died of pneumonia on the tenth postoperative day, and although no ulcer was found, erosion was present about the silk sutures. The five remaining dogs died in from twenty-two to fifty days with ulceration of the jejunum complicated by perforation or hemorrhage. Neumann, de Moor and Deloyers⁶³ achieved the same end by performing end to end anastomosis of the stomach and the jejunum, and instead of transplanting the common duct they ligated and anastomosed the gallbladder to the jejunum just distal to the gastrojejunal anastomosis. They did a one stage operation and noticed that the procedure was long and shocking. Of six dogs operated on, two presented definite ulceration, and jejunitis developed in two.

If an attempt is made to summarize or draw conclusions from this bewildering and confusing maze of contradictory experimental results, it is found that: 1. There is progressively diminishing immunity to the formation of ulcer from the duodenum aborally. 2. Probably the reflux of the entire duodenal contents of the stomach, particularly in the prepyloric region, will prevent the formation of ulcer or actuate healing if ulcer has already formed. 3. Deviation of the duodenal, biliary and pancreatic alkaline secretions will more consistently produce ulcer than

63. Neumann, F.; de Moor, P., and Deloyers, L.: Contribution à l'étude de la pathogénie des ulcères duodénaux. Dérivation des sucs duodénaux et pancréatiques dans l'iléon terminal, *Compt. rend. Soc. de biol.* **105**:892, 1930.

the isolated deviation of each. 4. Probably bile is more influential than pancreatic juice or duodenal secretion alone in the protection against the formation of ulcer. 5. Possibly the pancreatic juice is more effective than duodenal secretions alone in the prevention of the development of ulcer.

Because of the present day shadows cast on the experimental results by the overhead clouds of doubt, contradiction and insolvability, this investigation was attempted. One of the chief difficulties in attempting to draw conclusions is the somewhat risible, but almost exasperating, ability of two investigators performing the same procedure to obtain diametrically opposite results—witness Berg's and Elman and Hartmann's findings in deviation of pancreatic juice. Much of this diversity is due to comparisons made by different observers and under different circumstances. Thus, it would appear that if there is an equalization of extraneous factors, a much better basis for comparison could be made with the resulting stronger grounds for the drawing of conclusions. In the following experiments an attempt is made to evaluate the relative protective value of the constituents of the alkaline duodenal juices, viz., the succus entericus, the bile and the pancreatic juice. Each group of experiments is characterized by a similar procedure, so that they all have a common denominator. However, each group has one added change which may account for any difference in results obtained, as all the other factors are equal. Under such rigidly controlled experiments there can be little objection to comparisons, and more convincing conclusions can be drawn.

AUTHOR'S EXPERIMENTS

Material and Method.—Before any dog was used for the operative procedure it was first observed for a short time to determine with some degree of certainty that it was acclimated to the environment of the kennel. Only healthy, moderately large dogs, free from any evidence of distemper, infection or pregnancy, were used. In all of the surgical procedures the following postoperative routine was instituted. An intravenous infusion of warmed 5 per cent solution of dextrose containing normal lactate-Ringer solution was given into the external jugular vein immediately after the operation. The amount used was based on the dosage of 50 cc. per kilogram of body weight. Similar infusions were given once daily for the following three days. The next three days the dog was allowed to have water and was fed equal parts of milk and Karo corn syrup morning and afternoon. On the seventh postoperative day, it was returned to a normal stock kennel chow diet. Usually on the first or second postoperative day the dog appeared active, stood on its feet, wagged its tail and took a normal interest in the surroundings.

All the ulcers were studied microscopically in order to corroborate definitely the gross changes. Necropsy was performed immediately after the death of the dog, and the specimen was fixed at once in a large quantity of 10 per cent dilution of solution of formaldehyde U. S. P. or Zenker's fixative. General histopathologic study was performed by the utilization of the hematoxylin and eosin stain, and the study of evidence of increased fibrosis was facilitated by the use of Mallory's aniline blue stain.

In the consideration of the experimental findings of peptic ulceration it is always best to begin with a common understanding of the definition of terms. A distinction must be made between a mucosal erosion and a true peptic ulcer. Between the mucosa and the submucosa of the dog there is a prominent band of muscle referred to as the muscularis mucosae. Any localized mucosal defect extending only to or occasionally partially involving this muscularis mucosae is considered as an



Fig. 1.—Drawing of the completed operative procedure performed on the dogs in group 1. The pylorus was severed, and the gastric and duodenal ends were closed. Continuity was reestablished by anterior gastrojejunostomy.

erosion, whereas a true peptic ulcer is a mucosal defect which has penetrated the muscularis mucosae with its base well in the submucosa or resting on or partially involving the muscularis propria. Penetration through this muscularis propria and opening into the general peritoneal cavity or having a base formed by another viscus, such as the liver, spleen, pancreas or diaphragm, is referred to as a perforated ulcer (fig. 2).

Grossly the ulcers had the characteristics of the subacute and chronic ulcers in man. The ulcerated area was usually round, but occasionally oval, with the long axis parallel to the long axis of the intestines. Of particular interest is the site of the ulcer. In order to have a thorough and common understanding, a definition of terms is again apropos. A gastric ulcer is one found anywhere in the stomach proper. A jejunal ulcer is one located in the jejunum, usually near the gastrojejunal anastomosis (fig. 2). A gastrojejunal anastomotic ulcer is one situated at the suture line of anastomosis (fig. 3).

Microscopically, these ulcers resembled the typical subacute and chronic ulcers seen in man, although some of them had acute and sub-

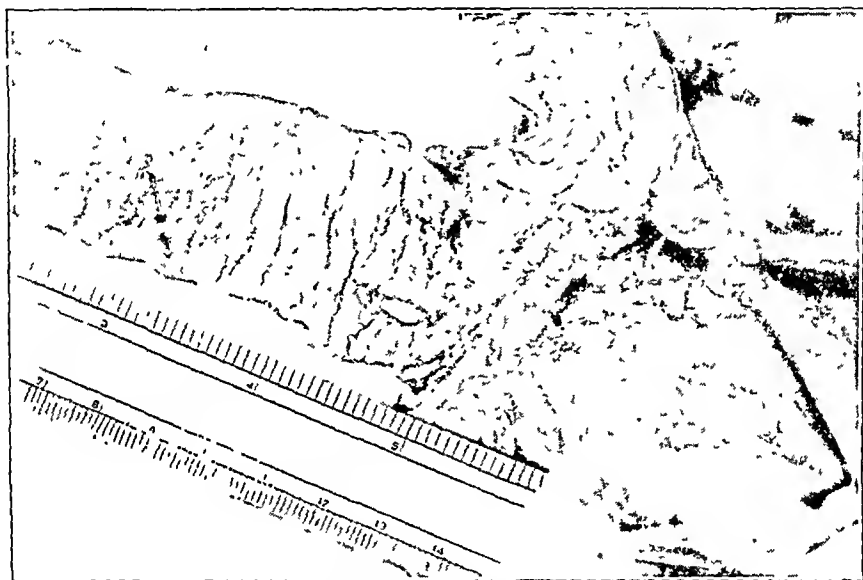


Fig. 2 (group 1, dog 54).—Pyloric occlusion and gastrojejunostomy were performed. Note the perforated ulcer in the efferent loop of the jejunum.

acute characteristics. The subacute ulcers were typified by rapid and deep penetration into the muscle layers with a steep wall (fig. 4). Frequently the process progressed so rapidly that adhesions had no time to form, and complete perforation resulted. In some the diameter at the mucosal level was greater than at the base, so that the edge of the ulcer had a sloping or terraced appearance. There was only a moderate fibroblastic reaction, with some lymphoid and round cell infiltration. Thrombosed vessels and hemorrhage were occasionally noted in the deeper layers. There was only a moderate amount of granulation tissue. In some there was a marked, acute inflammatory reaction about the crater with definite induration and leukocytic infiltration.

In the majority of chronic ulcers the crater was deep, involving all the muscular layers with a dense fibrotic base. This was excellently

demonstrated by the Mallory stain. The edges were definitely raised and somewhat overhanging. The thickness of the fibrotic base varied from a rather thin layer to a thick, dense, contracted base with some distortion. Frequently the wall of the ulcer on the proximal side was steep and markedly elevated, whereas the distal side appeared gently sloping. This characteristic is explained by Aschoff⁶⁴ as due to the passage of food across it, producing a slipping of the mucosa partly over the ulcer. On the inner surface there was usually present a layer of fibrin, necrotic tissue and cellular exudate, varying in thickness and depending on the existing degree of healing. The mucosa appeared

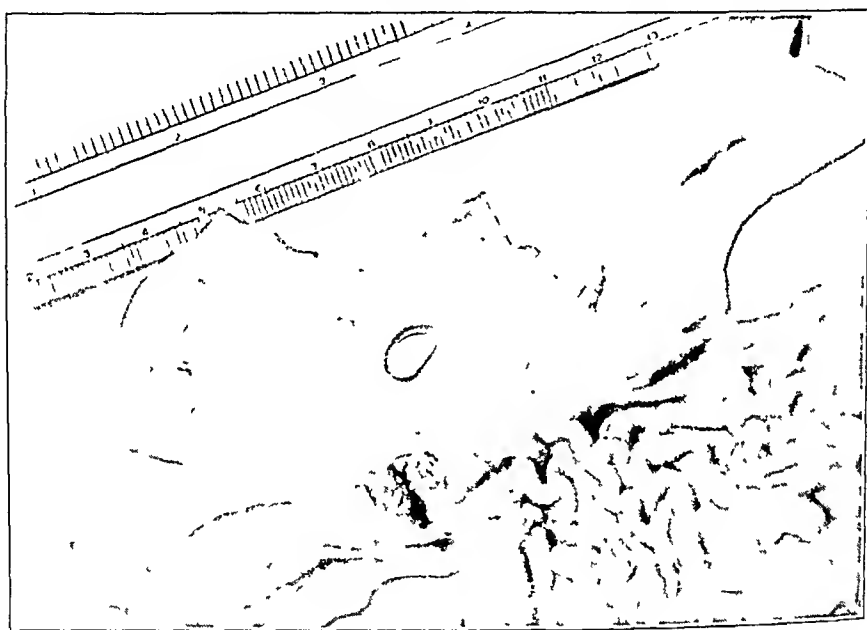


Fig. 3 (group 3, dog 68).—Pyloric occlusion, anterior gastrojejunostomy and transplantation of the common bile duct into the terminal portion of the ileum were performed. A perforated ulcer is shown in the efferent loop of the jejunum. Note also the anastomotic ulcer opposite the perforated ulcer. The anastomotic ulcer is of the chronic, fibrotic type. Two black silk sutures can be seen at the base of the ulcer hanging free into the lumen.

thickened, was definitely proliferated and produced a picture of an overhanging edge or recess formation beneath it, as a result of the sloughing away of the submucosa (fig. 4). The greatest thickening of the base was at the periphery, and the adjacent muscular wall appeared receded. Also in the periphery there was considerable lymphocytic and plasma cell infiltration in all the layers. A few mononuclear and polymorpho-

64. Aschoff, L.: Lectures on Pathology (delivered in the United States, 1924), New York, Paul B. Hoeber, Inc., 1924.

nuclear cells were seen in the mucosa and submucosa. Varying degrees of infiltrating granulation were always present beneath the exudative layer and at the periphery beneath the submucosa.

GROUP 1.—*Pyloric Occlusion and Gastrojejunostomy.*

Method.—With the dogs under ether anesthesia and rigid aseptic precautions, a right paramedian incision was made. Hemostasis in the wound was secured by ligation of bleeding vessels with no. 00 plain catgut. The pylorus and duodenum were delivered into the wound. The right gastric and right gastro-epiploic arteries were divided between clamps and ligated with no. 1 plain catgut. The site was then well packed off with wash cloths soaked in hot saline solution to catch any spillage. Crushing clamps were not used in any of the procedures. The pyloro-duodenal junction was divided, and both ends were closed by successively incising them for a small distance and closing the incisions with a hemostatic whip-over



Fig. 4.—Low power photomicrograph of a subacute jejunal ulcer. Note the recess formation beneath the epithelium on either side, resulting in the appearance of undermined edges. Perforation was prevented in this ulcer by the omentum, which sealed over the base of the ulcer on the serosal side. The base of the ulcer is shown as this omental covering.

suture of no. 00 chromic catgut. These ends were inverted by a continuous Lembert stitch of black silk. In order to reestablish continuity of the gastro-intestinal tract, an anterior gastrojejunostomy was performed. The jejunum just distal to the ligament of Treitz was delivered into the wound as well as the lower end of the corpus of the stomach. An isoperistaltic anastomosis was performed, the antimesenteric border of the jejunum being used. Two stay sutures of black silk were first introduced, approximately 3.5 cm. apart. The stoma was about 2.5 cm. in length. The hemostatic and serosal sutures consisted of no. 00 chromic catgut and black silk, respectively. The abdominal wound was closed by using a continuous black silk suture for the peritoneum and a similar suture for the sheath of the rectus muscle. The edges of the skin were approximated with a continuous interlocking stitch of black silk. This surgical procedure was usually performed in from forty-five to fifty minutes.

Results.—This group consisted of twenty dogs, which lived from nine to two hundred and seventy-one days after operation. Immediate recuperation from the operation in the majority of the animals was astonishingly rapid. However, after about the third postoperative week anorexia began to develop in some of the dogs, particularly those with ulceration, and they lost weight rapidly. Whereas those dogs in which ulcer was noted at autopsy lived an average period of forty-two days after operation, the dogs without ulcer had an average postoperative duration of seventy-four and four-tenths days. The average postoperative duration in days for the twenty animals was fifty-eight and two-tenths, or about two months.

In ten of the twenty dogs ulcer was not found at necropsy. Four dogs without ulceration died of pneumonia twenty, twenty-five, thirty-nine and sixty-nine days after operation, respectively, after sufficient time for the ulcer to develop had elapsed. Two of the animals died twenty-six and sixty-two days, respectively, after operation of an apparently unaccountable inanition. These dogs never maintained

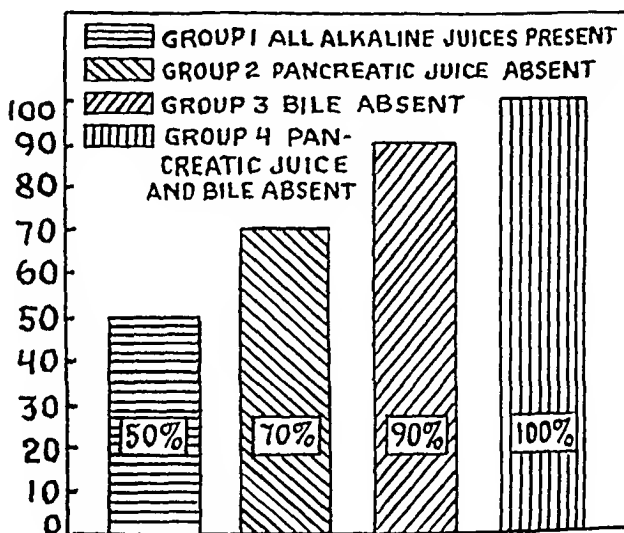


Fig. 5.—Graph showing the incidence of ulcer formation in the respective groups of dogs.

a normal appetite and about one week before death lost weight rapidly. Two other animals, which died forty-two days after operation, had a somewhat similar clinical manifestation but at necropsy presented evidence of a massive gastrointestinal hemorrhage. The stomach, jejunum and ileum and even the upper portion of the colon were filled with old blood, some of which appeared altered. The exact cause of this could not be definitely determined. However, it was believed to be due to gastritis and jejunitis as the mucosa in this region showed some congestion and small petechial areas. One dog, dying one hundred and fifty-five days after operation, had in the right ventricle a large number of dirofilaria, which was in all probability the cause of death, as no other abnormalities were found. The last animal of this group was still in good health two hundred and seventy-one days after operation, at which time it was finally killed, but no lesion was found.

In the remaining ten dogs, or 50 per cent, ulcer developed (fig. 5). All of the ulcers were of the typical subacute and chronic type. The shortest postoperative duration in this group was nine days, the longest one hundred and four days and

the average forty-two days, or six weeks. Of the ten dogs with ulceration, there were seven, or 70 per cent, which died of perforation and general peritonitis (fig. 2). Another dog presented a perforated ulcer, which was plastered against the liver and had eroded into it. One dog, dying fifty-three days after operation, showed no evidence of perforation or other complication. The tenth dog died one hundred and four days after operation of intussusception of the ileum with an associated mesenteric thrombosis. Besides this, there were two jejunal ulcers present.

There were only two dogs, or 20 per cent, of the ten in which more than one ulcer developed, and in each of these there were two ulcers. These ulcers varied in size from 0.5 to 2 cm., but in the majority they were approximately 1 cm. in diameter.

In the group of ten dogs all the ulcers were jejunal and located at approximately the same site, i. e., in the efferent loop of the jejunum opposite the anastomosis on the antimesenteric border slightly anteriorly (fig. 2). The consistency of this characteristic location demands some explanation. There is certainly no reason to attribute this to trauma, because this would be expected to occur in the jejunum immediately opposite the anastomosis rather than in the efferent loop. A more plausible and attractive explanation is the chemical theory. The alkaline duodenal contents in draining down the intestine must pass from the afferent side of the anastomosis toward the efferent loop. No neutralization with gastric chyme occurs until the alkaline juices encounter the acid chyme opposite the anastomosis. Thus, the afferent loop and that portion of the jejunal mucosa opposite the anastomosis are protected by the normal alkaline juices. However, the greater degree of this neutralization has occurred when the alkaline juices have reached the efferent loop, and little alkalinity remains to protect this portion of the jejunal mucosa, thus there being greater likelihood of the development of ulceration.

GROUP 2.—Pyloric Occlusion, Gastrojejunostomy and Deviation of Pancreatic Juice.

Method.—In this group of dogs the effect of the deviation of pancreatic juice was determined. The same procedure as that used on group 1 was performed, but in addition the main pancreatic duct was transplanted into the terminal portion of the ileum in the following manner (fig. 6). The small accessory pancreatic duct, which enters the duodenum about 0.5 cm. below the papilla of Vater, was identified and divided between ligatures. The larger, main pancreatic duct, which enters the duodenum about 4 cm. below the papilla of Vater, was identified and reamed out of the duodenum so that there remained attached to its os approximately 2 cm. of duodenal mucosa, submucosa, muscularis and serosa. The resulting defect in the duodenum was immediately closed with a single row of Lembert's sutures. A loop of ileum was then brought up and a site chosen about 30 mm. from the ileocecal junction. Two black silk sutures were introduced through its medial wall into the lumen and out through a small stab wound in the opposite side of the bowel. These sutures were then passed through the small margin of the wall of the duodenum surrounding the os of the pancreatic duct and brought back through the stab wound to cross the lumen and emerge through the wall of the ileum near their origin. By carefully pulling these sutures taut, the pancreatic duct was drawn through the stab wound and into the lumen of the ileum. It was secured in place by tying these sutures. In order to avoid any undue tension on the sutures holding the pancreatic duct in the lumen, the ileum was approximated to the duodenum by a few Lembert sutures. This surgical procedure was usually performed in approximately fifty-five minutes.

Results.—This group consisted of ten dogs, which lived from seven to fifty-six days after operation. Rapid immediate recovery from the operation with maintenance of normal appetite and weight characterized all the animals. It was not until about one week before they succumbed that they began to show loss of appetite, rapid decline in weight and progressive weakness and apathy.

The shortest postoperative duration was seven days, the longest fifty-six days and the average thirty-four and six-tenths days. Three dogs, dying fifteen, seventeen and thirty-eight days postoperatively, showed no evidence of ulceration in the stomach, duodenum or jejunum. In each instance the cause of death could not be definitely determined at necropsy and was attributed to inanition. The transplanted

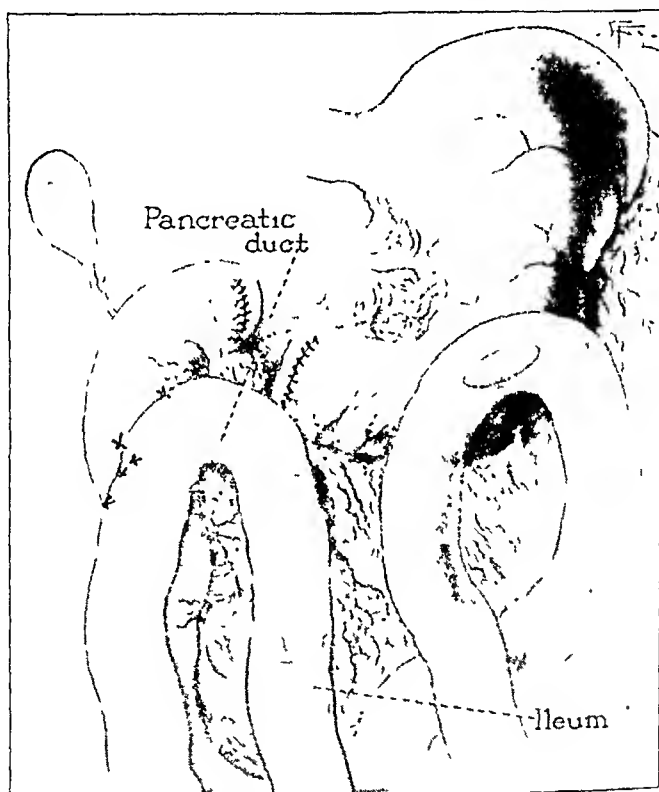


Fig. 6.—Drawing of the completed operative procedure performed on the dogs in group 2. The pylorus was severed, and the gastric and duodenal ends were closed. Continuity was reestablished by anterior gastrojejunostomy. The accessory pancreatic duct was ligated and severed, and the main pancreatic duct was transplanted into the terminal portion of the ileum.

pancreatic duct was found to be patent and apparently functioning satisfactorily. The pancreas was grossly normal; microscopic study revealed no abnormal changes. Careful dissection of the pancreas from the duodenum was performed in every instance at necropsy to exclude the possibility of some pancreatic secretion still draining into the duodenum.

Of the ten dogs in this group, there were seven in which ulcer developed, an incidence of 70 per cent (fig. 5). Five of the seven had perforated ulcers, with resulting peritonitis. In two there was no perforation, but a large amount of blood was found in the gastro-intestinal tract, much of which appeared altered.

The ulcers ranged in size from 1 to 2 cm. in diameter and were usually round or oval. In four instances (57 per cent) there was more than one ulcer present (fig. 7). Of particular interest in this group is the variation in position of the ulcer. In two animals anastomotic ulceration in the efferent portion of the suture line was present. The first dog, dying fifty-one days after operation, had two ulcers, one in the efferent loop of the jejunum of the subacute variety and the other in the suture line. The anastomotic ulcer was of the chronic variety, with thick, indurated, overhanging edges and a hard, fibroblastic base, with two loose black silk sutures hanging free from the center. In six of the seven dogs there was an ulcer in the efferent loop of the jejunum in approximately the same location as in group 1. In one instance there were two ulcers in the efferent loop of the jejunum



Fig. 7 (group 2, dog 96).—Pyloric occlusion, anterior gastrojejunostomy and transplantation of the pancreatic duct into the terminal portion of the ileum were performed. Two subacute and chronic ulcers are shown in the efferent loop of the jejunum. One ulcer has perforated. Note that these ulcers lie immediately opposite each other and appear as mirror images of each other, except that one has perforated. This is referred to as a "contact" or "kissing" ulcer.

exactly opposite each other, or the "kissing" type, one of which perforated (fig. 7). In only one dog, dying forty-six days after the operation, there was an ulcer immediately opposite the stoma, and in this instance there were two other ulcers of the subacute variety lying just caudad or in the jejunum on the efferent side of the stoma. Of more than passing interest, because it was not observed in the previous group, was the occurrence of ulcers in the jejunum on the efferent side of the stoma. Both of these were of the acute and subacute types. However, in one of these dogs, dying fifty-six days after operation, another large ulcer of the chronic variety was found in the efferent loop of the jejunum, as in group 1.

GROUP 3.—*Pyloric Occlusion, Gastrojejunostomy and Deviation of Bile.*

Method.—The same procedure as that used on Group 1 was performed, but in addition the common bile duct was transplanted into the terminal portion of the ileum in the following manner (fig. 8): The common bile duct was identified and dissected free for approximately 2 cm. at its distal end. Two mosquito forceps were applied to the duct just proximal to its entrance in the duodenum, and it was sectioned between these. The distal end was doubly ligated with black silk. The proximal end was then split upward for about 2 mm., and mosquito forceps were applied to each "lip." A loop of the terminal portion of the ileum was brought up, and a site about 20 cm. from the ileocecal junction was chosen. Two black silk sutures were introduced through its medial wall into the lumen and

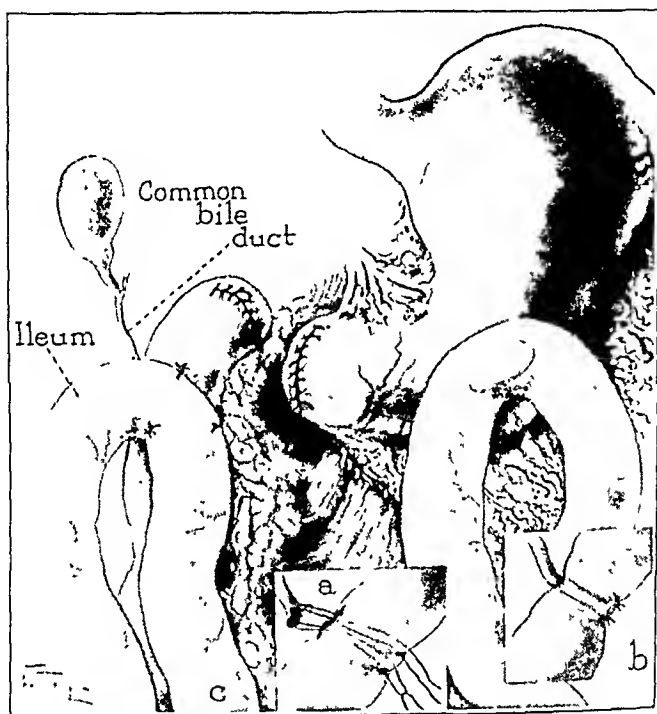


Fig. 8.—Drawing of the completed operative procedure performed on the dogs in group 3. The pylorus was severed, and the gastric and duodenal ends were closed. Continuity was reestablished by gastrojejunostomy. Note the drawings in the lower right corner, illustrating the technic of transplantation of the common bile duct into the terminal portion of the ileum. (The pancreatic duct was transplanted by a similar technic.) In *a*, two black silk sutures have been introduced through the medial wall of the ileum into the lumen and out through one of the "lips" of the split common bile duct and then brought back through the stab wound to cross the lumen and emerge through the wall of the ileum near the origin of the suture. In *b*, the common bile duct has been drawn through a stab wound into the lumen of the ileum and secured by tying the sutures.

out through a small stab wound placed in the opposite side. Each suture was passed through one of the "lips" of the split common bile duct and then brought back through the stab wound to cross the lumen and emerge through the wall of the ileum near the origin of the suture (fig. 8*a*). By carefully pulling these

sutures taut, the common bile duct was drawn through the stab wound into the lumen of the ileum and then secured by tying the sutures (fig. 8*b*). In order to avoid any undue tension on the sutures holding the common duct in the lumen, the ileum was approximated to the duodenum by a few Lembert sutures. At autopsy the ducts were carefully dissected and found to have healed satisfactorily (fig. 9). This surgical procedure usually required about fifty-five minutes.

Results.—This group consisted of twenty dogs, which lived from seven to sixty days after operation. The majority of the animals recovered from the operation rapidly and maintained normal appetite and weight for a short period of time, and then anorexia, progressive loss of weight, evidences of inanition and weakness began to develop, and the animals eventually died. In contrast to the animals in

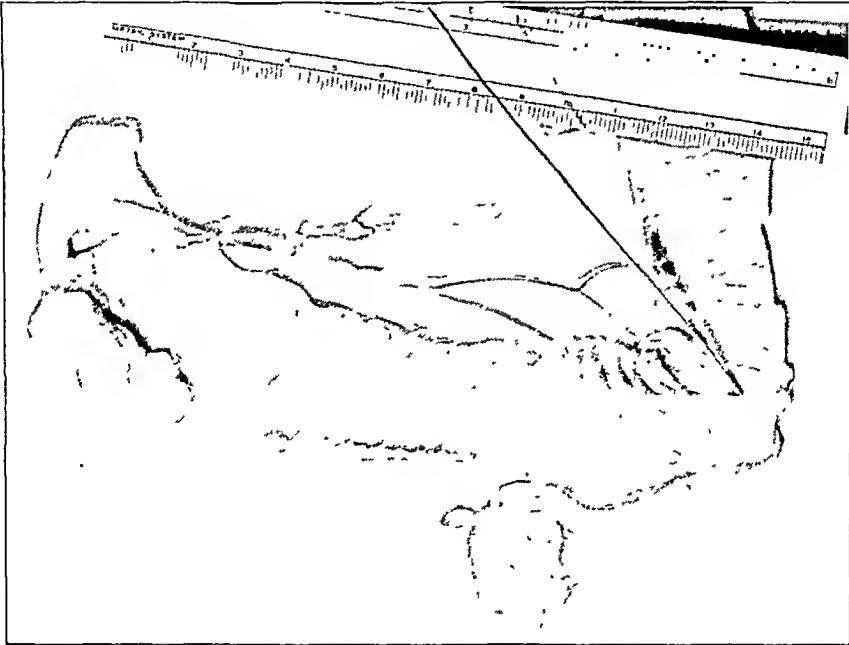


Fig. 9 (group 3, dog 74).—Pyloric occlusion, anterior gastrojejunostomy and transplantation of the common bile duct into the terminal portion of ileum were performed. The photograph shows the terminal portion of the ileum and the transplanted common bile duct. Straw has been passed through opening of transplanted duct in the wall of the ileum. Note the cecum and the appendix at the extreme right of the picture.

group 1, for which the average postoperative duration of life was fifty-eight and two-tenths days, or about two months, the postoperative duration for this group was twenty-nine and eight-tenths, or about one month. This difference is sufficiently pronounced to be of some significance and will be discussed later.

Two of the dogs, dying nineteen and forty-two days, respectively, after operation, presented no evidence of peptic ulceration. However, in the latter, an unusually large number of intestinal worms were found in the jejunum and ileum. The jejunum, ileum and cecum and the upper portion of the colon were literally packed with blood, some of which appeared to be altered. When the mucosa was washed clean, the heads of the worms were found embedded in the mucosa, which

appeared congested with many small petechial areas. In all probability, this was the cause of the massive oozing of blood. The other dog also presented clinically inanition and toxemia, and at necropsy massive gastro-intestinal hemorrhage was also found. The mucosa of the stomach, duodenum and jejunum appeared congested with petechial areas scattered throughout. Gastritis and jejunitis were undoubtedly present, but no obvious erosion or ulcerations.

Of the twenty dogs in this group, ulcer developed in eighteen, or 90 per cent (fig. 5). All of the ulcers were of the typical subacute and chronic type. The

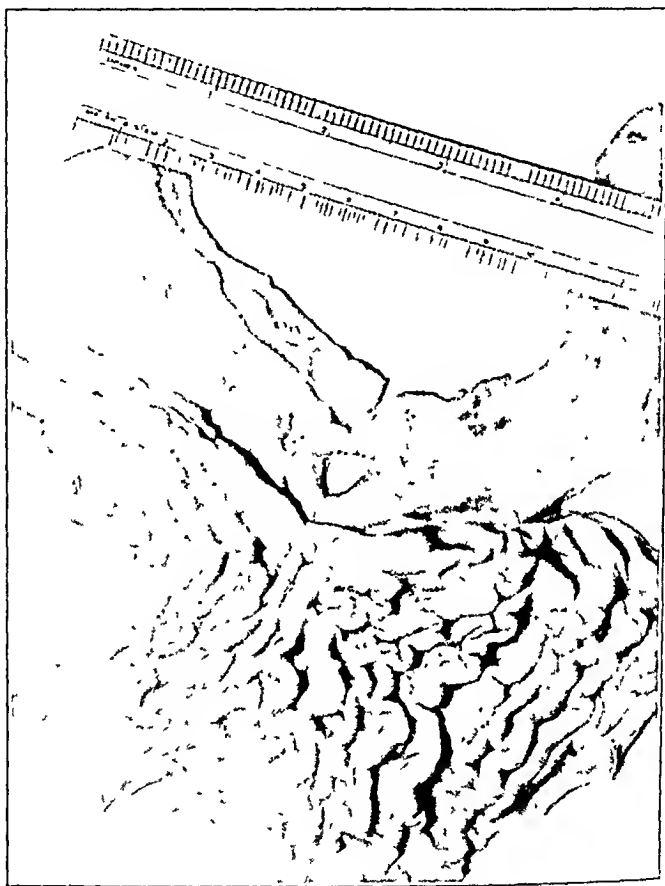


Fig. 10 (group 3, dog 79).—Pyloric occlusion, anterior gastrojejunostomy and transplantation of the common bile duct into the terminal portion of the ileum were performed. Two ulcers of the jejunum are shown, one of which has perforated. Note that one ulcer is immediately opposite the stoma, and the other is in the efferent loop. There is only a small margin of jejunal mucosa between the two ulcers.

shortest postoperative duration was seven days, the longest sixty days and the average about thirty days. Perforation occurred in thirteen of the eighteen dogs, an incidence of 72.2 per cent. Perforation into the general peritoneal cavity with resulting peritonitis occurred in ten of the thirteen dogs (fig. 10). Necropsy on two of the animals, dying twenty-two and twelve days postoperatively, respectively, revealed interesting changes. In both animals the anterior wall of the jejunum

at the site of the gastrojejunostomy was found adherent to the left leaf of the diaphragm, and the jejunal ulcer had ruptured through the diaphragm into the left pleural cavity, with resulting pleurisy and pneumonia. The remaining animals with a perforating ulcer also revealed an interesting observation. The jejunal ulcer was intimately adherent to one lobe of the liver and had perforated into this viscus with erosion of its parenchyma. In one dog, which died of pneumonia seven days after operation, a large subacute jejunal ulcer had already developed, thus revealing how early an ulcer may occur. One dog, dying only thirteen days after

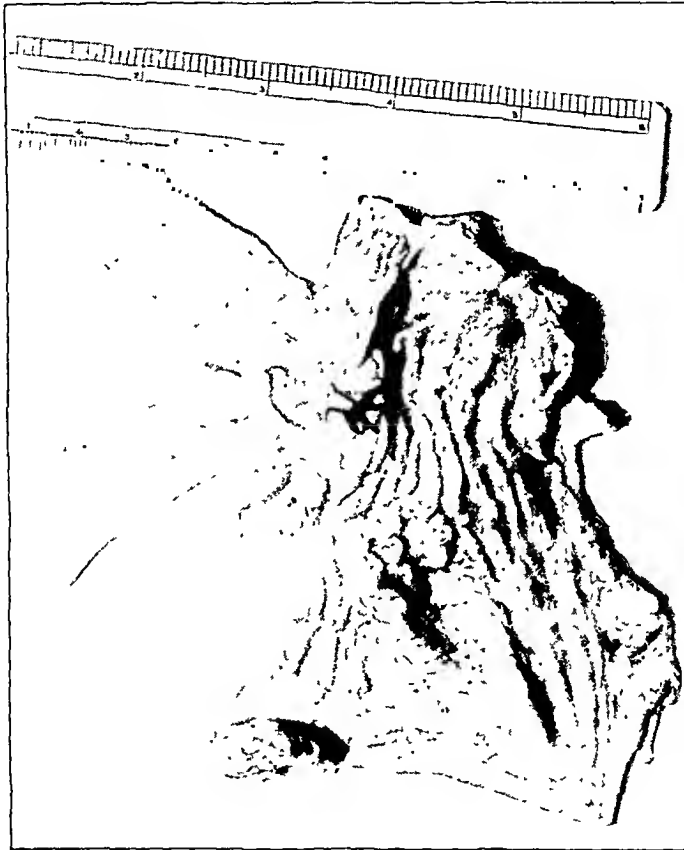


Fig. 11 (group 3, dog 71).—Pyloric occlusion, anterior gastrojejunostomy and transplantation of the common bile duct into the terminal portion of the ileum were performed. A large, chronic, fibrotic ulcer is shown, which has perforated. Note that the ulcer is in the jejunum immediately opposite the stoma and that there is a margin of normal jejunal mucosa between the ulcer and the anastomotic suture line. Also note that in the anastomotic suture line opposite the ulcer there are two black silk sutures lying free, but no associated ulcer.

operation, already presented a typical chronic ulcer with a dense fibrotic base. This ulcer microscopically revealed evidence of healing by the encroaching tongue of epithelium over the fibrotic base. The remaining three dogs had characteristic subacute and chronic ulcer with a hemorrhagic base and gross evidence of hemorrhage in the gastro-intestinal tract.

Of pertinent interest is the unusual finding of black silk sutures lying free in the base of the anastomotic ulcer in two of the dogs (fig. 11). As in all the operations, no. 00 chromic catgut was used for the hemostatic suture and black silk for the seromuscular suture. This associated occurrence of ulcer is in direct contrast to the observations of Hosoi,⁶⁵ in which loose threads were found hanging in the lumen but with no evidence of associated ulceration in six instances. This contradictory finding will be discussed later.

Of the eighteen animals in which ulcer developed, thirteen showed a single ulcer and five had two ulcers. Thus, in this group there was only a slight increase of approximately 8 per cent over the 20 per cent incidence of multiple ulcers in

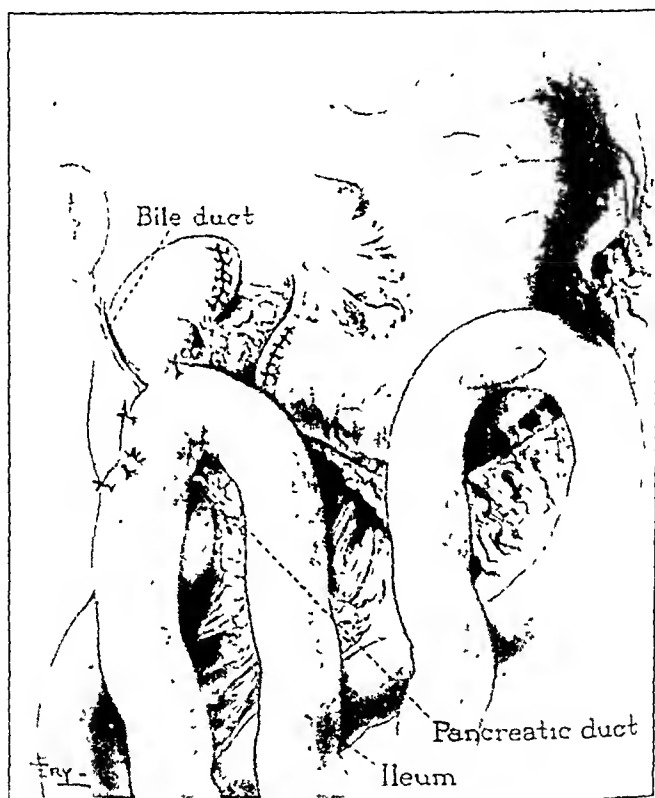


Fig. 12.—Drawing of the completed operative procedure performed on group 4. The pylorus was severed, and the gastric and duodenal ends were closed. Continuity was reestablished by anterior gastrojejunostomy. The accessory pancreatic duct was ligated and severed. The main pancreatic duct and the common bile duct were transplanted into the terminal portion of the ileum.

group 1. The ulcers varied in size from 0.4 to 1.5 cm. in diameter. They were usually round or oval, with characteristic indurated, overhanging margins or with some undermining of the edges. Analysis of the site of the ulcers reveals some interesting facts. In thirteen of the eighteen dogs in which ulcer occurred the location was in the efferent loop of the jejunum, as in group 1. In six of the

65. Hosoi, K.: Peptic Ulceration: Its Relationship to Gastro-Intestinal Chemism, Thesis, 1934.

eighteen dogs (33.3 per cent) the ulcer was situated in the jejunum directly opposite the stoma, usually on the antimesenteric side (figs. 2 and 11). Of the six, there were two in which two ulcers were present, in each of which the other ulcer occurred in the efferent loop of the jejunum, as in group 1. In four of the eighteen dogs (22.2 per cent) an anastomotic ulcer was present in the suture line, with loose black silk hanging from the base in two instances. In two of these four animals there was another ulcer in the jejunum opposite the stoma in one and in the efferent loop of the jejunum in the other. In no instance was an ulcer found in the afferent loop of the jejunum. One dog, dying of a perforated ulcer and peritonitis fifty-seven days after operation, demonstrated the development of a biliary calculus. At the opening of the transplanted common bile duct into the wall of the terminal portion of the ileum there was present one of the black silk sutures, and on its end there was a round dark brown biliary calculus.

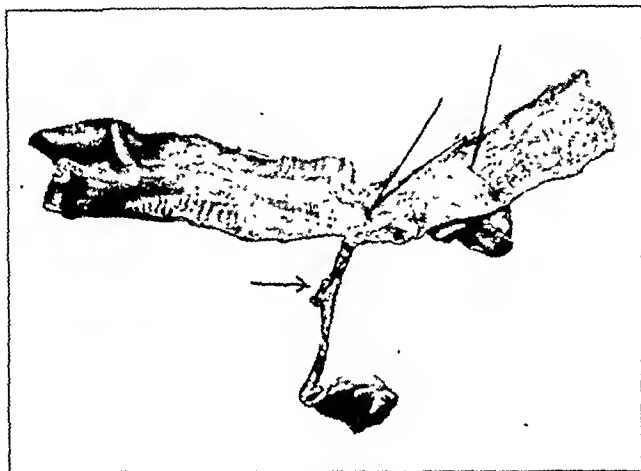


Fig. 13.—Photograph of the opened terminal portion of the ileum with straws passing through the opening of the transplanted pancreatic and common bile ducts. The arrow points to the end of the straw, showing through the opening made in the common bile duct.

GROUP 4.—Pyloric Occlusion, Gastrojejunostomy and Deviation of Bile and Pancreatic Juice.

Method.—The same procedure as that used on group 1 was performed, but in addition both the common bile duct and the main pancreatic duct were transplanted into the terminal portion of the ileum (fig. 12). The same technic was used for transplanting the ducts as was used for groups 2 and 3, respectively. The common bile duct was transplanted approximately 5 cm. above the pancreatic duct (fig. 13). The small accessory pancreatic duct was always sought and if identified was severed and ligated so that no pancreatic juice entered the duodenum. At autopsy it was definitely determined that no pancreatic juice had entered the duodenum. The foregoing surgical procedure rarely required more than one hour and thirty minutes and was frequently performed in sixty or seventy minutes.

Results.—This group consisted of ten dogs, which lived from twelve to fifty-one days after operation. Although the animals had a rapid immediate recuperation from the operation, they rarely maintained a normal appetite and weight except for a short time. In the majority of instances, after about the second post-

operative week they began to evince anorexia, rapid loss in weight and general decline, with marked weakness and apathy. The shortest postoperative duration was twelve days, the longest fifty-one days and the average about twenty-five days, or three and a half weeks.

Ulceration occurred in all the animals. This was complicated by perforation with resulting peritonitis in five, or 50 per cent. In one dog, which died of pneumonia seventeen days after operation, a chronic ulcer had already developed. In four instances the ulcers were subacute and chronic, with marked gastrointestinal hemorrhage. Whereas in group 2 there was an incidence of multiple ulcer of 57 per cent, in this group there was an incidence of only 20 per cent. The ulcers varied in size from 0.4 to 2.5 cm. in diameter.

Here again there is a slight variability in the location of the ulcers although not as pronounced as in group 2. In two dogs, dying fifty-one and twenty-one days, respectively, after the operation, a chronic ulcer was found in the afferent loop of the jejunum. In the dog dying twenty-one days after operation there was another ulcer in the jejunum on the efferent side of the stoma which had perforated. In the dog dying fifty-one days after operation only one ulcer was present, and this was of the chronic type. In nine of the ten dogs the ulcer was in the efferent loop of the jejunum, and in one of these there were three ulcers present successively, alined with about 0.5 cm. of normal mucosa separating them. There was no anastomotic ulcer in any of the dogs.

COMMENT

The basic procedure used on the four groups of dogs is nothing more or less than the von Eisberg⁶⁶ type of operation, in which the pylorus is sectioned and the gastric and duodenal ends closed with reestablishment of continuity by gastrojejunostomy (fig. 7). This was all that was done on the first group of animals, but for each of the other three groups there was one added change, i.e., the deviation of pancreatic juice in the second group, the deviation of bile in the third and the deviation of both pancreatic juice and bile in the fourth group. Thus any difference in results obtained in each group may be accounted for by the added change.

Of the first group of twenty dogs, in which pyloric occlusion and gastrojejunostomy alone were performed, jejunal ulcer developed in 50 per cent. This is a slightly higher incidence than is usually reported and is worthy of some consideration. Why should ulcer develop at all after this procedure? The physiology of the gastro-intestinal tract does not seem to be altered to such a commensurable degree. There is no deviation of alkaline juices. The gastric acidity should not be increased. It would appear that the best possible explanation is that the jejunal mucosa is functionally unable to receive acid gastric chyme, and this factor is relatively more pronounced after this procedure, as the pyloric occlusion does not permit a regurgitation of the alkaline duodenal juices into the stomach to help neutralize the gastric acidity. However,

66. von Eisberg, quoted by Alvarez.¹⁴

it must be remembered that the latter factor is debatable. Ivy and Fauley⁶⁷ have clearly demonstrated the differences existing between the duodenal and the jejunal mucosa in their respective abilities to cope with acid gastric chyme. They performed the "surgical duodenal drainage" operation, which was modified by leaving an inch or so of duodenum attached to the pyloric end of the stomach. Ulcer always developed in the jejunal mucosa, although the duodenal mucosa was subjected to the same force of impinging gastric juice. Of course, in the procedure under consideration the traumatic factor (Mann and Williamson; McCann) of the propulsive nozzle-like action is certainly minimized, and it is necessary to resort to the chemical theory and the lessened resistance of the jejunal mucosa to explain the high incidence of the occurrence of ulcer.

Another interesting factor revealed by this series of experiments is the characteristic site of the ulcer, i. e., in the efferent loop of the jejunum. This seems to confirm the theory of acidity. The afferent loop is to a certain extent protected by the alkaline duodenal juices, as in their passage downward they reach the afferent side of the anastomosis first and exert the greatest degree of neutralizing power. However, after passing the stoma they lose to a great extent this acid-neutralizing power, and the jejunal mucosa of the efferent loop is exposed to acid gastric chyme of relatively higher acidity.

The incidence of ulcer formation here (50 per cent) is apparently somewhat higher than is usually reported. Alvarez⁷¹ reported a general incidence of 25 per cent. Clinical reports of incidence reveal a marked variance of from 1 to 2 per cent (Moynihan⁶⁸) to as high as 52 per cent (Hurst and Stewart⁶⁹). According to Lewisohn,⁷⁰ Lamson⁷² and Strauss, Bloch and Friedman,⁷² an incidence varying from 2.5 to 34 per cent has been reported. Of course, these incidences are not quite comparable, as the procedure in these instances does not usually entail pyloric occlusion, and the subject operated on is not normal. Nevertheless, an incidence of from 25 to 50 per cent is to be expected, and the number observed here is not altogether out of proportion.

Of the second group of ten dogs, in which an operation similar to that used on the animals in group 1 was performed but with the addi-

67. Fauley, G. B., and Ivy, A. C.: Experimental Jejunal Ulcer, *Proc. Soc. Exper. Biol. & Med.* **27**:182, 1929. Footnote 36.

68. Moynihan, B.: Treatment of Duodenal Ulcers, *Lancet* **1**:631, 1923.

69. Hurst, A. F., and Stewart, M. J.: Jejunal and Gastrojejunal Ulcers, *Lancet* **2**:742, 1928.

70. Lewisohn, R.: Frequency of Gastrojejunal Ulcers, *Surg., Gynec. & Obst.* **40**:70, 1925.

71. Lamson, O. F.: Gastrojejunal Ulcer, *S. Clin. North America* **13**:95, 1933.

72. Strauss, E. E.; Bloch, L., and Friedman, J. G.: Gastrojejunal Ulcer: Medical and Surgical Considerations, *J. A. M. A.* **90**:181 (Jan. 21) 1928.

tion of deviation of the pancreatic juice into the terminal portion of the ileum, typical subacute and chronic ulcer developed in seven animals (70 per cent). The factors involved in the experiment on this group are exactly similar to those involved in the experiment on group 1, except that there was a deviation of pancreatic juice, so that there were only two alkaline duodenal juices remaining to protect the jejunum, viz., succus entericus and bile. A mathematical comparison revealed that ulcer occurred in a 20 per cent higher incidence in group 2 than in group 1. In other words, deviation of pancreatic juice produced ulcer in 20 per cent of instances, which indirectly indicates its protective influence against the formation of ulcer. This is slightly in contrast to the observations made by Neumann, Deloyers and de Moor⁷³ and Berg and Jobling.⁵⁴ These findings are somewhat in agreement with those of Elman and Hartmann,⁵⁰ who found ulcer in each of six dogs in which there was a continued loss of total pancreatic juice. On the other hand, Neumann, Deloyers and de Moor⁷³ and Berg and Jobling⁵³ found that pancreatic juice exerted little, if any, protective influence against ulcer formation. The results obtained in my experiments fall between these two extremes. Pancreatic juice undoubtedly plays a definite protective rôle in the prevention of the formation of peptic ulcer, and the 20 per cent higher incidence of ulceration in this group as compared with the incidence in group 1 irrefutably justifies this statement. Besides the ulceration which occurred at the usual sites in the efferent loop of the jejunum, it was present in the anastomotic line, in the jejunum opposite the stoma and in one instance in the efferent loop. In the dogs in the first group in which there was no deviation of the alkaline duodenal juices, ulcer occurred in a characteristic site, i. e., the efferent loop of the jejunum. Ulcer never occurred in the more unusual sites, such as the afferent loop of the jejunum, the anastomotic suture line and the jejunum opposite the stoma. These unusual sites are proximal to the usual sites, i. e., the efferent loop of the jejunum.

Of the third group of twenty dogs, in which an operation similar to that used on group 1 was performed but with the addition of deviation of bile into the terminal portion of the ileum, typical subacute chronic ulcer developed in eighteen, an incidence of 90 per cent. Here again, all the factors involved in the experiment on group 1 apply, except the deviation of the pancreatic juice. In this group the incidence of ulcer was 40 per cent higher than the incidence in group 1 (fig. 5). The procedures used on the two groups of animals were the same, with the exception that in group 3 bile was excluded from the anastomotic site. It is therefore apparent that the bile exerts a protective influence on the jejunal mucosa as regards the formation of ulcer when this is exposed to acid gastric chyme. In other words, deviation of bile pro-

73. Neumann, Deloyers and de Moor, footnotes 26 and 55.

duced ulcer in 40 per cent of instances, which indirectly indicates its protective influence against the formation of ulcer. This is in accordance with the results obtained by Kapsinow⁵⁹ and Neumann, de Moor and Deloyers.⁵⁵ That bile is probably the most influential constituent of the alkaline duodenal juices has been the opinion of the majority of experimental investigators.

Of particular interest in this group is the occurrence in two of the dogs of black silk sutures hanging free in the base of the anastomotic ulcer. Suture material was used only on the outside row of the sero-muscular suture. Judd⁷⁴ reported nonabsorbable suture material still present in the ulcer in nine of fifty-five cases, or 16.25 per cent, in which the operation had originally been performed at the Mayo Clinic, and in seventeen of forty-six cases in which gastrojejunostomy had been performed elsewhere. Valdoni⁷⁵ observed sixty-one peptic ulcers post-operatively, of which six had old silk sutures lying loose at the bottom of the ulcer. He subsequently made an experimental study on dogs to determine the mechanical effect of nonabsorbable suture material and concluded that it is an important local predisposing cause of a post-operative ulcer. Walton⁷⁶ recorded nine of twenty cases in which a portion of suture was present at the base of the ulcer. On the other hand, Sistrunk⁷⁷ and Moynihan⁶⁸ reported cases in which suture material was found hanging from the stoma for many years with no ulceration. Hosoi,⁶⁵ in experimental observation on fifty-seven dogs, noted black silk suture hanging free from the suture line in six instances, with no evidence of anastomotic ulceration. Lewisohn⁷⁰ expressed the belief that the type of suture material used is not important. In all probability the tendency has been to stress this factor unduly. It will be observed that there were six of the eighteen ulcers (33.3 per cent) that occurred in the jejunum immediately opposite the stoma. There were also four anastomotic ulcers (22.2 per cent), and two of these contained pieces of bright silk thread hanging free from the base. The presence of these ulcers in as high an incidence as 33.3 and 22.2 per cent, respectively, demands some explanation. Neither type of ulcer was present in group 1. Undoubtedly the explanation is to be found in the chemical theory, as it is impossible to overlook the fact that the only difference between the dogs in group 1 and those in group 2 is the absence of bile in the latter. Ulceration occurred more readily in the latter group because there was an absence of an influential and undeniably effective acid-neutralizing agent. Although in the anasto-

74. Judd, E. S.: *Jejunal Ulcer*, Surg., Gynec. & Obst. **33**:120, 1921.

75. Valdoni, P.: *Relation Between Postoperative Ulcer and Presence of Threads of Silk on Neostomy*, Policlinico (sez. chir.) **39**:571, 1932.

76. Walton, A. G.: *Gastrojejunal Ulcer*, *Lancet* **2**:800, 1925.

77. Sistrunk, quoted by Hurst and Stewart.⁶⁹

motie ulcer there was present a chronically irritating and traumatic factor in the nonabsorbable suture material, it became sufficiently pronounced to produce ulcers only when there was the added influence of inadequate neutralizing power of the alkaline duodenal secretion. That bile has a greater protective influence than pancreatic juice in preventing the development of ulcer is clearly demonstrated by the comparative incidences of ulcer in group 3 (90 per cent) and group 2 (70 per cent). This induces me to concur with the opinions of Berg, Johnston and Jobling⁶² that bile exerts a greater protective influence than pancreatic juice in the prevention of the formation of peptic ulcer and to disagree with Elman and Hartmann and their associates,⁵⁷ who opine that the protective power of pancreatic juice is greater. On the other hand, I cannot agree with the opinion of the former investigators, that pancreatic juice is of little or no importance in the prevention of ulcer, or with the view of the latter, that bile is of little or no consequence.

In group 1, in which there was no deviation of the alkaline duodenal juices, ulcer occurred in a characteristic site, i. e., the efferent loop of the jejunum. Ulcer never occurred in the more unusual sites, such as the afferent loop of the jejunum, the anastomotic suture line and the jejunum opposite the stoma. These unusual sites are proximal to the usual sites, i. e., the efferent loop of the jejunum. The occurrence of ulcer in these more proximal locations occurred only when one of the alkaline juices, bile or pancreatic juice, was deviated, thus indicating that under these circumstances there is a less adequate neutralization of acid gastric chyme. The fact that they occurred more frequently in group 3 (deviation of bile) than in group 2 (deviation of pancreatic juice) indicates that bile exerts a greater acid-neutralizing power.

If the protective influence of bile and pancreatic juice is attributed to their alkalinity or their acid-neutralizing powers, the correlation of the findings of Jones⁷⁸ becomes interesting. This author aseptically collected bile and pancreatic juice from five dogs, titrated twenty-four hour specimens with tenth-normal hydrochloric acid and determined the p_H with a quinhydrone electrode. He observed that pancreatic juice was usually more alkaline (p_H from 7.8 to 9) than hepatic bile (p_H from 7.4 to 8.5). However, he stated that hepatic bile may be as alkaline as pancreatic juice, as the two act in a compensatory manner, but that the amount of pancreatic juice secreted is more than that of bile when both are flowing freely. He also found that the buffer action is due to sodium bicarbonate, a substance common to both secretions. Boldyreff³⁰ found bile from the gallbladder to have a percentage of alkalinity (sodium carbonate, Na_2CO_3) of 0.05, as compared with that of pancreatic juice, 0.65.

78. Jones, K. K.: Comparison of Buffer Value of Bile and Pancreatic Juice Secreted Simultaneously, *Proc. Soc. Exper. Biol. & Med.* **28**:567, 1931.

In the fourth group there were ten dogs, in which an operation similar to that used on group 1 was performed except that the pancreatic and common bile ducts were both transplanted into the terminal portion of the ileum. In this procedure there was only the duodenal secretion to protect the sensitive jejunal mucosa. There was an incidence of ulcer of 100 per cent. Such an extremely high incidence indicates complete absence of protective influence. This is in accord with the experience of Mann and Williamson,⁶ Mann and Kawamura⁴² and Grey,⁴³ who performed duodenectomy and concluded that the duodenum is apparently not essential to life. It would appear that the combined elimination of bile and pancreatic juice will result in a higher incidence of ulcer than their elimination singly or the exclusion of one or the other in combination with the duodenal secretion. This is in contrast to the opinion of Bauer and Aron,⁴¹ who maintained that duodenal secretions exerted the greatest protective influence.

It will be noted that in this group there were no anastomotic ulcers, and in only one animal was there an ulcer only in the afferent loop. This is not in accord with the findings in groups 2 and 3. From the results in the latter groups, a higher incidence of ulcer at these unusual sites would be expected. The only explanation that can be offered for this is that possibly the dogs died sooner and as a result ulcer did not have time to develop, as it will be noticed that the average postoperative period for these dogs was twenty-five days as compared with forty-two days and thirty-four and six-tenths days for the animals in groups 2 and 3, respectively. It must be admitted, however, that it is a rather weak explanation.

GENERAL SUMMARY AND CONCLUSIONS

A review of the voluminous literature which has now accumulated on the relative protective value of the alkaline duodenal juices in preventing the formation of ulcer has served to give some comprehension of the bewildering maze of confusion that now exists. It has been suggested that this diversity of opinion and the contradictory experimental results have been due in great measure to the fact that observations and comparisons have been made by different investigators under varied and different circumstances. Because of the present day difficulty in drawing conclusions from the confused and risibly contradictory experimental results, this investigation was made. The experiments were performed in such a manner as to permit without criticism the drawing of conclusions from the results obtained. The dogs used in the investigation were divided into four groups. In the first group the pylorus was severed, and the gastric and duodenal ends were closed. Continuity was reestablished by anterior gastrojejunostomy. The same procedure was performed on the second group, but with the addi-

tion of ligation and division of the accessory pancreatic duct and transplantation of the main pancreatic duct into the terminal portion of the ileum. The third group of animals was subjected to the same procedure as the animals in first group, but with the addition of transplantation of the common bile duct into the terminal portion of the ileum. The fourth group was also subjected to the same procedure as the first, but with the addition of transplantation of both the bile and the pancreatic duct into the terminal portion of the ileum. Obviously the procedures used on all the animals are similar with the exception of one factor, the deviation of pancreatic juice in the second group, the deviation of bile in the third, and the deviation of both bile and pancreatic juice in the last group. Thus, because of the excellent comparability of the procedures used on the four groups any difference in results obtained can be accounted for by the one different factor characterizing each experiment. In this manner more convincing conclusions can be drawn.

A total of sixty dogs was used in the four groups. Twenty animals were used in the first group, ten in the second, twenty in the third and ten in the fourth. In the first group, which served as controls, the basic operative procedure performed consisted of severance of the pylorus with closure of both ends and anterior gastrojejunostomy. The twenty dogs operated on lived from nine to two hundred and seventy-one days, and subacute and chronic ulcer developed in ten, an incidence of 50 per cent. In the ten dogs in which ulcer developed, perforation and peritonitis occurred in seven. The ulcers were grossly and microscopically similar to ulcers occurring in man. All the ulcers developed at a characteristic site, i. e., in the jejunal mucosa of the efferent loop. The explanation for this high incidence of ulcer after this procedure and the characteristic location is that the jejunal mucosa has little resistance to the acid gastric chyme, and the efferent loop of the jejunum is bathed with gastric chyme of relatively higher acidity than the efferent loop or the jejunal mucosa immediately opposite the stoma.

The same operative procedure was performed on the second group of dogs as on the first group, except that the main pancreatic duct was transplanted into the terminal portion of the ileum, and the accessory pancreatic duct was sought and if found severed and ligated. In this group of ten dogs the incidence of ulcer was 70 per cent. Except for the deviation of the pancreatic juice in this group, all other factors were equal to those involved in the experiment on group 1, yet ulcer developed in the former in a 20 per cent higher incidence than in the latter. This difference in results obtained in these two groups must be accounted for by the only different factor, i. e., the absence of the alkaline pancreatic juice. This seems to justify the conclusion that pancreatic juice exerts a definite protective influence against the formation of jejunal ulcer.

The third group of animals was subjected to the same operative procedure as the first group, except that the common bile duct was transplanted into the terminal portion of the ileum. Of twenty dogs operated on in this group, typical subacute and chronic ulcer developed in eighteen, an incidence of 90 per cent. Except for the deviation of bile in this group, all other factors were equal to those involved in the experiment on group 1, yet ulcer developed in the former in a 40 per cent higher incidence than in the latter. This marked difference in results obtained in the two groups of dogs must be accounted for by the only different factor in the two groups, i. e., the absence of bile in the alkaline duodenal secretions. Another difference in the results obtained in this group is the occurrence of ulcer in the anastomotic suture line in four instances, with pieces of black silk suture hanging free from the base of two. Still another difference is the occurrence of ulcer in the jejunal mucosa immediately opposite the stoma. The high incidence of these ulcers (anastomotic, 22.2 per cent, and opposite the stoma, 33.3 per cent) proximal to the usual site in the efferent loop emphasizes more strongly the acid-neutralizing influence of the bile. As compared to the incidence in group 2, on which the same procedure was performed except that pancreatic juice was deviated instead of bile, there was a 20 per cent greater incidence of ulcer. It will also be observed that in group 3 ulcer occurred in a slightly greater frequency in the more unusual sites (anastomotic suture line and in the jejunum opposite the stoma) than in group 2. These two differences indicate that bile exerts a greater acid-neutralizing power than pancreatic juice.

The fourth group of dogs was subjected to the same operative procedure as the first group, except that the common bile duct and main pancreatic duct were both transplanted into the terminal portion of the ileum. The accessory pancreatic duct was always sought and if found severed and ligated. Of ten dogs operated on, typical subacute and chronic ulcer developed in all. Except for the deviation of bile and pancreatic juice, all the factors, were equal to those pertaining to group 1, yet ulcer developed in a 50 per cent higher incidence. This indicates that the succus entericus has little or no protective influence in the prevention of ulcer.

A graphic representation of a comparison of the results obtained in the four groups is illustrated in figure 5. These results seem to justify the following conclusions: 1. Of all the constituents of the alkaline duodenal juices, bile has the most significant and effective influence in preventing the formation of jejunal ulcer; (2) the duodenal secretion, the succus entericus, is the least important, and (3) the pancreatic juice is midway between the two in this respect.

HISTOLOGIC STUDIES ON THE FATE OF DEEPLY IMPLANTED DERMAL GRAFTS

OBSERVATIONS ON SECTIONS OF IMPLANTS BURIED FROM ONE
WEEK TO ONE YEAR

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This series of experiments was conducted to determine the advisability of filling a depression by burying a free section of dermis and fat underneath the skin. Eitner¹ in 1920 described a method of elevating a depression of the face by inserting a free section of deepithelized derma beneath the skin overlying the depression. He reported a case of paraffinoma of the cheek in which a depression resulted from the removal of the paraffinoma. Eitner removed the epidermis from a hairless portion of the abdomen with a Thiersch knife and excised a section of dermis and underlying fat. This he transplanted under the skin of the cheek. He observed the patient for about eight months and reported a completely satisfactory result. He apparently removed the epidermis for the purpose of insuring sterility of his transplant, but in this article he did not mention the possibility of the formation of a cyst. Vilray Blair and J. B. Brown used dermal grafts and described the method to Straatsma, who successfully used the graft to repair saddle nose.² Eagleton, Swain and Peer³ have successfully repaired large depressions in the forehead resulting from the removal of the frontal sinuses and the adjacent frontal bone by inserting a large graft of dermis, fat and fascia lata beneath the scalp. One patient on whom such a procedure was carried out was followed four years and showed no evidence of the formation of a cyst. Such a formation theoretically might occur from the hair follicles, sebaceous glands or sweat glands in the buried section of dermis. We considered it advisable, therefore, to determine experimentally the fate of epithelial derivatives in the dermis before advocating the use of the buried dermal graft. Our previous experience

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1. Eitner, E.: Ueber Unterpolsterung der Gesichtshaut. *Med. Klin.* **16**: 93 (Jan. 25) 1920.

2. Straatsma, C. R.: Use of the Dermal Graft in the Repair of Small Saddle Defects of the Nose, *Arch. Otolaryng.* **16**:506 (Oct.) 1932.

3. Eagleton, W. R.; Swain, R., and Peer, L. A.: Unpublished data.

had shown that dermis buried beneath the skin undergoes little reduction in thickness and hence is superior to fat alone, which is greatly reduced through absorption and partial replacement. The bulk of the graft, when desirable, may also be increased by using a number of dermal strips placed one over the other and held together by mattress sutures of plain catgut. This method of repair has achieved little popularity because of the theoretical possibility of the formation of cysts from sweat glands, hair follicles and sebaceous glands in the dermis or from remnants of epidermis incompletely removed from the surface of the dermis.

PREVIOUS EXPERIMENTAL WORK

Many investigators have performed experiments on animals by burying strips of epidermis and full thickness skin. In these experiments cysts were observed originating from the epidermis and from the hair follicles. In man, so far as we know, the investigation has been limited to the observation of traumatic epithelial cysts resulting from injury or following an operative incision. Reverdin⁴ expressed the belief that as a result of trauma bits of epidermis were torn off and deposited deeply in the corium and that cysts developed from these implanted grafts.

Garré⁵ stated that the implantation of epidermis alone produced a smooth-walled cyst, while in the cyst resulting from implantation of a whole thickness skin graft papillae were also present.

Kaufmann⁶ produced a cyst beneath the skin of the cock's comb by making an oval incision deeply through the skin and suturing the margins of the skin together over the oval section. The buried epidermis gradually took on a rounded form and invariably developed into a cyst. The origin of this cyst from the epidermis was evident, because the cock's comb contains no hair follicles or glandular elements to provide another possible source.

Schweninger,⁷ in a similar experiment on dogs, produced a subcutaneous cyst by burying a piece of skin below the surface. Some of the cysts so produced contained hairs and sebaceous glands in their walls and fat, cholesterol and epidermal scales within the lumen.

4. Reverdin, J. L.: Des kystes epidermiques des doigts, *Rev. méd. de la Suisse Rom.* **7**:121, 1887.

5. Garré, C.: Ueber traumatische Epithelcysten der Finger, *Beitr. z. klin. Chir.* **11**:524, 1894.

6. Kaufmann, E.: Ueber Enkatarrhaphie von Epithel, *Virchows Arch. f. path. Anat.* **97**:236, 1884.

7. Schweninger, E.: Beitrag zur experimentellen Erzeugung von Hautgeschwulsten (Atheromen). *Charité ann.* **11**:642, 1884.

Pels-Leusden⁸ suggested another possible origin for the epithelial cyst and supported it by experiments on the ears of rabbits. He made an incision through the skin, using a "sharp knife" to prevent the accidental implantation of epidermis during the operation. He then placed an absorbable magnesium disk deeply within the corium. A cyst was produced about the foreign body, the lining membrane of which contained all the layers of normal epidermis. Pels-Leusden expressed the belief that such a cyst was formed by proliferation from the epithelium of glands that were unavoidably injured by the incision. He thought it unlikely that in an ordinary injury the tough skin of the palm could be torn off and implanted.

Hesse,⁹ in a series of experiments, buried a magnesium disk, catgut and a blood clot beneath the skin and later examined histologic serial sections of the sites of implantation. He demonstrated that epithelization to produce a cyst may take place from the hair follicles and glandular epithelium without any apparent burial of epidermis. He was unable to find papillae in the wall of any of the cysts produced, however, and he stated that for the development of papillae the implantation of whole thickness skin was necessary.

Davis and Traut¹⁰ produced epithelium-lined tubes and sacs in dogs by transplanting free whole thickness skin grafts directly onto one of the abdominal muscles. In each animal the fascia was drawn over the graft, and the graft was left in place from twenty to forty days. The animal was killed, and the buried skin with adjacent structures was carefully removed and fixed in formaldehyde. The authors noted the formation of an epithelium-lined tube or cyst resulting from a cylindric growth at the margins of the skin graft. They stated that when the experiments were carried beyond forty days maceration of the epithelial lining of the cavity of the cyst occurred. They assumed that this is due to pressure from the content of the cyst. The fate of hair follicles and glandular elements in the dermis of the skin graft is not histologically described.

Zimches,¹¹ in a series of his own experiments and in experiments with Wassiljew, buried free strips of full thickness skin in the muscle

8. Pels-Leusden, F.: Ueber abnorme Epithelisierung und traumatische Epithelcysten, *Deutsche med. Wchnschr.* **31**:1340, 1905.

9. Hesse, F. A.: Die Entstehung der traumatischen Epithelcysten, *Beitr. z. klin. Chir.* **80**:494, 1912.

10. Davis, J. S., and Traut, H. F.: The Production of Epithelial Lined Tubes and Sacs, *J. A. M. A.* **86**:339 (Jan. 30) 1926.

11. Zimches, J. L.: The Fate of Surface Epithelium Transplanted into Deeper Tissues and Its Relation to Epithelial Cysts, *Frankfurt. Ztschr. f. Path.* **42**:203, 1931.

of dogs. His conclusions based on implants buried up to two years were as follows:

(a) The epidermis of the implanted skin curves in the shape of a horseshoe, and on about the twenty-fifth day the ends of the horseshoe join, forming a circle or closed cavity lined by epithelium.

(b) The cavity of the cyst is partly filled by epithelial débris and broken-down hairs.

(c) The cyst continues to grow because the lining epithelium constantly produces cornified epithelium, which is pushed into the lumen.

(d) Smaller cysts may develop from the epithelium of hair follicles.

(e) The tendency of surface epithelium, when transplanted into other tissue, to bend on itself and form a closed cavity represents a definite law and finds its explanation in the general growth law of epithelium.

(f) Changing of one kind of epithelium into another or into malignant tissue was never found in these experiments.

(g) The implanted section of skin heals in its new position and quickly joins the surrounding tissue by means of granulation tissue, which is later organized into connective tissue.

The occurrence of foreign body giant cells in the unlined wall of an epidermal cyst has been explained by Stewart.¹² According to him, the contents of the cyst, whether hair, fat, cholesterol or epithelial débris, have the irritant properties of a foreign body. In those parts of the cyst where the epithelial lining is lacking, this irritation produces a type of granulation tissue rich in giant cells.

Wien and Caro¹³ stated that the traumatic epithelial cyst is believed to develop as a result of injury to the skin and occurs most frequently on exposed sites, such as the palms and fingers. The probable origin of the cyst is from epidermis torn from the surface and carried into the corium. Such a cyst may also form about a foreign body implanted into the dermis by proliferation of epithelium from the hair follicles or glandular elements of the skin.

The foregoing experiments were conducted on animals and dealt with the production of an epidermal cyst by the transplantation of epidermis into other tissues and with the production of a cyst from hair follicles when a full thickness section of skin was implanted or when a foreign body was introduced into the dermis.

12. Stewart, M. J.: On the Occurrence of Irritation Giant Cells in Dermoid and Epidermoid Cysts, *J. Path. & Bact.* **17**:502, 1912.

13. Wien, M. S., and Caro, M. R.: Traumatic Epithelial Cysts of the Skin, *J. A. M. A.* **102**:197 (Jan. 20) 1934.

Our work was done on human beings. Free sections of skin and fat from which the epidermis had apparently been removed were buried beneath the skin of the chest and removed for histologic examination at intervals of from seven days to twelve months. These experiments were possible because of the large number of rib graft operations performed in our service at the Newark Eye and Ear Infirmary. When a rib graft operation for saddle nose is done, the excess portion of the rib cartilage is stored beneath the skin of the chest for future use in case the nasal graft becomes infected. If infection does not develop, the rib cartilage in the wall of the chest is removed and scrapped. Hence in our experiments it was possible to insert free sections of dermis and fat beneath the skin of the chest together with the rib cartilage and remove them at various intervals following successful operation on the nose.

EXPERIMENTAL PROCEDURE

A free elliptic section of skin and subcutaneous fat was removed from the abdomen of a number of patients on whom a rib graft operation was performed for the repair of saddle nose. The epidermis was shaved from each section as completely as possible with a sharp no. 11 Bard-Parker knife blade, and the remaining dermis and fat were inserted beneath the skin of the chest with the dermis outermost. At intervals of seven days, fourteen days, twenty-one days and two months, seven months and twelve months each implant was excised together with the overlying skin of the chest and placed in Zenker's solution. After an implant was sectioned in the usual manner, the tissues were stained with hematoxylin and eosin, and after examination they were photographed under high and low power magnification.

DESCRIPTION OF SECTIONS

The sections here described were prepared by Mr. David J. McKinnon, of the Newark Eye and Ear Infirmary. They represent various stages of the transplanted dermis from the abdomen.

Six stages are represented, as follows: one week, two weeks, three weeks, two months, seven months and one year. The most striking feature in the sections was the persistence of the apparently removed epidermis, which was definitely present in the four earlier sections and may have been present in the two later sections. The latter showed certain features which might indicate a temporary persistence of the epidermis.

The next observation which struck the eye was the difference in behavior between the two kinds of glands present in the dermal implant. The only surviving sebaceous gland was found in the section of the implant buried for one week; none was discovered in any of the later sections. On the other hand, the sweat glands were apparent in the implants of all stages, although the later sections showed them to be considerably changed.

The other striking observation concerns the reaction of the subcutaneous connective tissue of the site of the chest to the dermal implant. This was most pronounced in the middle stages but was found in some degree in all stages. It was a chronic inflammatory reaction of the granulomatous type, with the formation of granulation tissue containing beside the usual young capillaries and young fibroblasts, a large number of mononuclear cells and their derivatives. These are lymphocytes, macrophages and epithelioid or endothelioid cells (these both differing from macrophages mainly in being closely packed together) and giant cells.¹⁴ The last, although large multinuclear cells, are believed to be derivatives of the mononuclear epithelioid cells. These cells were either diffusely arranged or distributed in the form of granulomatous nodules of microscopic size containing all the aforementioned types of mononuclear cells, together with foreign bodies,

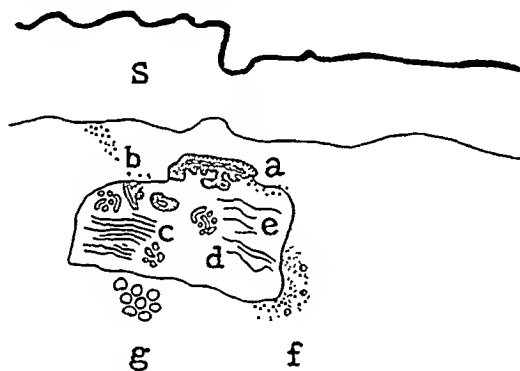


Fig. 1.—Diagram of a dermal implant at one week. *S* indicates the overlying skin of the chest; *a*, a flat epithelial cyst; *b*, a hair follicle with a sebaceous cyst; *c*, an empty hair follicle; *d*, sweat gland tubules; *e*, collagenous fibers of the implant; *f*, granulation tissue, and *g*, fat.

to be later described, the whole being surrounded by a fibrous capsule.¹⁵ The cause of this type of reaction, we believe, is particulate in nature and organic in chemical composition, but not microbic.

In the first section (figs. 1 and 2) we found the rather square rectangular implant well demarcated from the surrounding tissue, lying a little below the overlying skin. Immediately beneath the area of the incision, at the upper border of the implant, there was a small flat epithelial cyst or cleft (fig. 3). On its lower surface the papillae were well marked, the epidermis showing marked irregularity along its lower border and a cross-section of a hair follicle. The upper border, although showing almost as many layers of stratified squamous epithelium, presented no processes and showed no papillae along its outer border. The epithelial cyst or cleft contained some thin plates of horny material.

14. A similar type of cellular reaction was found by Zimches after implantation of dog's skin into muscle.

15. The granulomatous nodule is not mentioned by Zimches, only the diffuse type of cellular reaction.

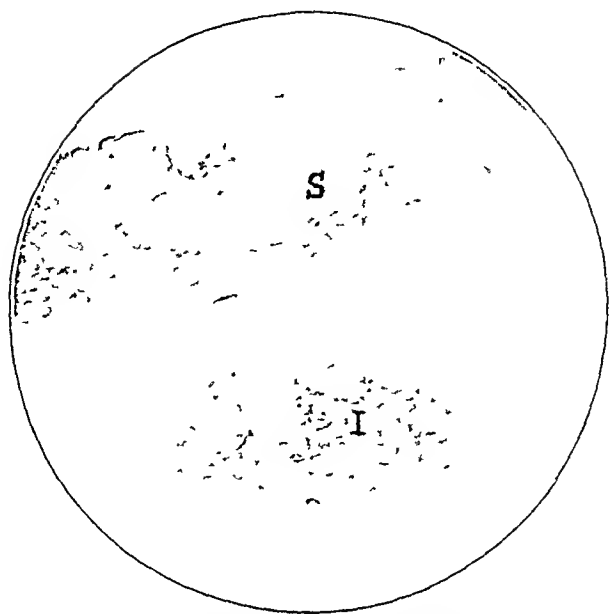


Fig. 2.—Section of a dermal implant at one week, showing the location beneath the skin of the chest; $\times 10$. *S* indicates the skin of the chest, and *I*, the dermal implant

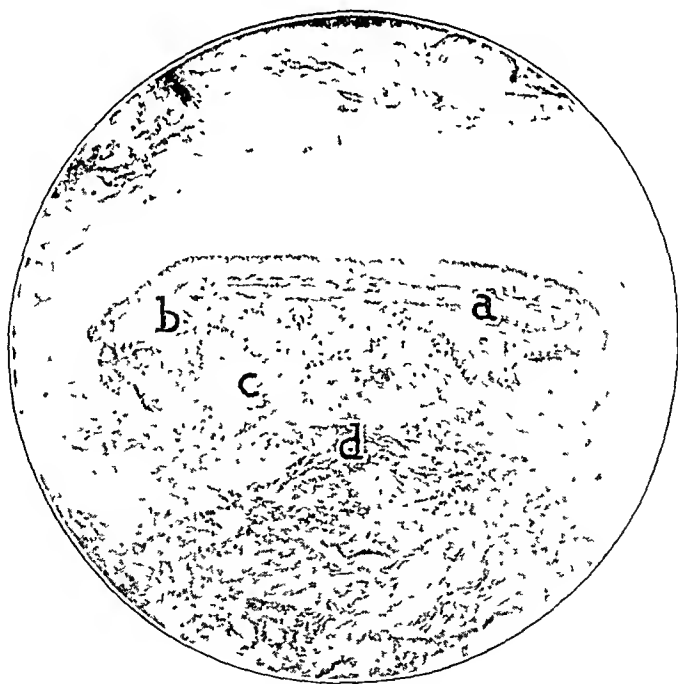


Fig. 3.—Section of a dermal implant at one week, showing a flat epithelial cyst, originating from the epidermis of the implant; $\times 100$. The cavity of the cyst is indicated by *a*, the epithelium lining cyst by *b*, the papillae beneath the epithelium of the floor of the cyst by *c* and a hair follicle, cut across, by *d*

The foregoing observations are considered as determining that the epithelial cyst or cleft has developed from a small area of epithelium inadvertently left on the dermal implant. The presence of well marked papillae along the lower border is the criterion, since it is generally held, as previously mentioned, that papillae do not develop under regenerated epithelium. We concluded, therefore, that the epithelial cleft or cyst developed from the epidermis of the implant.

To the left and below the epithelial cleft there was a small oval epithelial island with a small cavity and rather thick walls of stratified squamous epithelium. The cavity contained no hair or horny material.

In one area of the implant, along the upper border, a hair root with its follicle and a definite sebaceous gland was found (fig. 4). The cells of the gland were not well preserved, suggesting that it was already deteriorating. This assumption is borne out by the fact that no sebaceous glands were found in the later sections, although such negative evidence cannot be taken as finally conclusive.

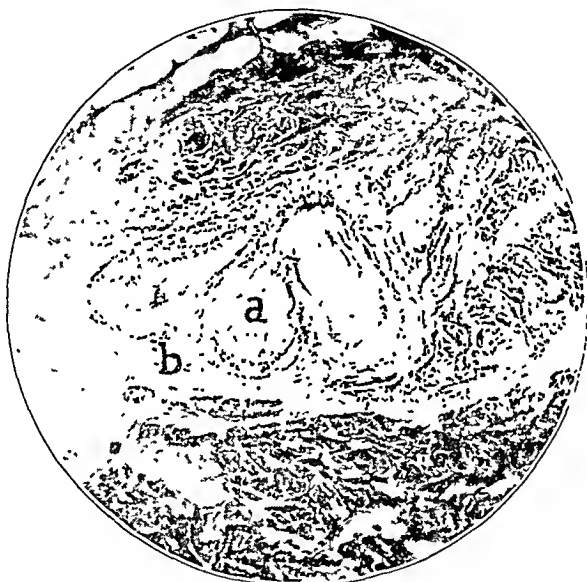


Fig. 4.—Section of a dermal implant at one week, showing a surviving sebaceous gland with a hair follicle; $\times 100$. The sebaceous gland is indicated by *a* and the hair follicle by *b*.

Scattered throughout the dense collagenous fibers of the dermis were numerous well preserved sweat gland tubules (fig. 5). There was no apparent increase in the fibroblasts of the dermis.

Beneath and to each side of the implant was found the normal adipose subcutaneous connective tissue. This was not everywhere present in contact with the implant. In certain regions its place was taken by granulation tissue. One strand of this tissue connected the upper border of the implant with the overlying skin. On the lower right corner of the implant the granulation tissue contained a number of giant cells. This tissue will be described more fully in later sections.

The section of the implant buried for two weeks was similar to that of the implant buried for one week in its relation to the overlying skin (fig. 6). In form

it represented an elongate rectangle bent downward at both ends. It showed no epithelial cyst, but near its upper border toward the left there was a small solid island of epithelium evidently derived from the dermal implant (fig. 7). In this island the cells were arranged in orderly fashion, with the basal layer cylindric. There was no horny layer or other layers to be differentiated. The cells appeared healthy and normal. The only other cells of epithelial derivation observed in this implant were those of the fairly numerous tubules of the sweat glands, some of which were not so well preserved as in the previous section, being thinner and poorly stained, though normal in relation to surrounding tissue.

The dense connective tissue of the dermal implant appeared normal. This implant showed a few deeply placed collagenous fibers surrounded by granulation tissue.

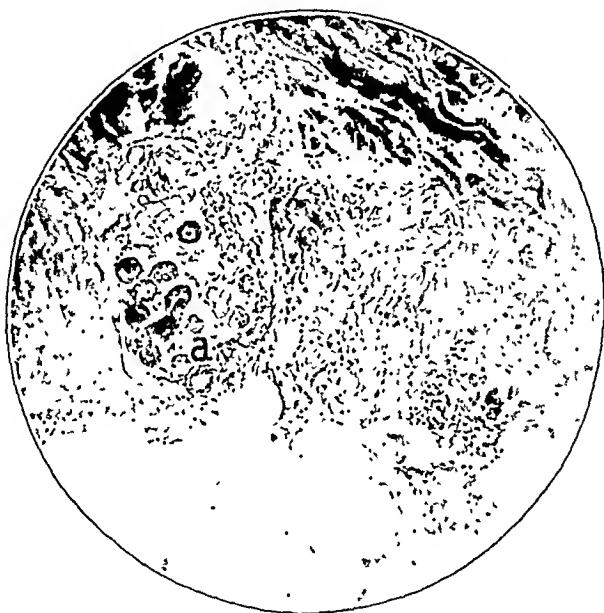


Fig. 5.—Section of a dermal implant at one week, showing the surviving sweat gland tubules of the implant; $\times 100$. The sweat gland tubules are indicated by *a* and the collagenous fibers of the implant by *b*.

The section showed a marked increase in the granulomatous reaction of the connective tissue (fig. 6*c*). The implant was practically surrounded by fresh granulation tissue, containing numerous diffusely distributed lymphocytes, macrophages, epithelioid cells and a considerable number of giant cells. The granulation tissue was most dense and the giant cells most numerous at the upper left angle of the implant. A thick strand of young connective tissue connected the upper surface of the implant with the overlying skin. Another area of the same mononuclear type of granulation tissue adhered to the right margin of the implant and a deep strand ran below, between which and the lower border of the implant normal adipose connective tissue, probably belonging to the implant, was seen. Such adipose tissue, probably belonging to the site of implantation, was seen above the implant, between it and the skin.

In the section of the implant buried for three weeks the implant was situated nearer to the overlying skin, being separated only by a narrow area filled with young fibrous and granulomatous tissue (fig. 8). On the upper left margin it was separated definitely from the overlying skin by the normal subcutaneous adipose

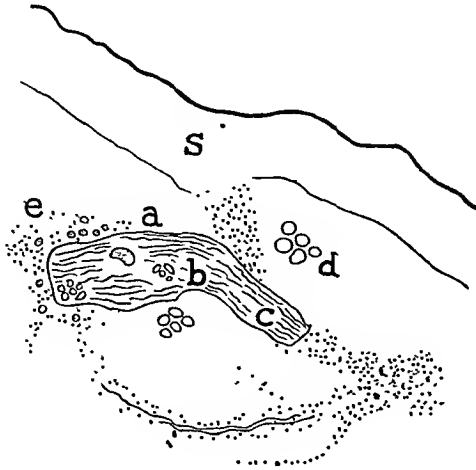


Fig. 6.—Diagram of a dermal implant at two weeks. *S* indicates the overlying skin of the chest; *a*, the epithelial island, originating from the epithelium of the implant; *b*, the sweat gland tubules; *c*, the collagenous fibers of the implant; *d*, fat, and *e*, granulation tissue surrounding the implant, containing giant cells.



Fig. 7.—Section of a dermal implant at two weeks, showing an epithelial island (*a*), originating from the epidermis of the implant; $\times 100$.

layer. In this region the upper border of the implant showed a definite and comparatively large flat oval epithelial cyst (fig. 9). The lower border showed papillae with one long sharp process of epithelium extending downward from the basal

layer. The cavity of the cyst was flat and contained horny material. The upper wall of the cyst was smooth and showed no papillae at its outer margin.

At about the same level, close to the upper margin, there was an elongate hair follicle containing its hair root cut in diagonal section. Space existed between the hair and the follicle cells, which was partly filled with horny material. Farther

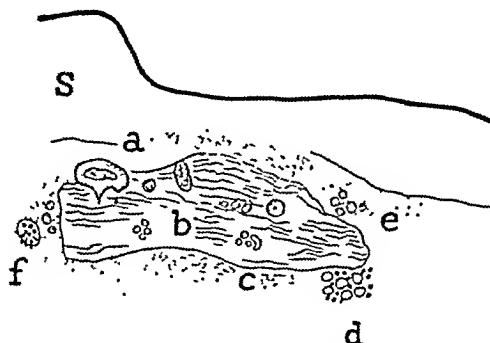


Fig. 8.—Diagram of a dermal implant at three weeks. An epithelial cyst, containing horny material is indicated by *a*; hair follicles, one of which is forming a small cyst, by *b*; sweat gland tubules by *c*; fat, in process of replacement by mononuclear cells, by *d*; granulation tissue, containing giant cells, surrounding the implant, by *e*, and a granulomatous nodule by *f*.

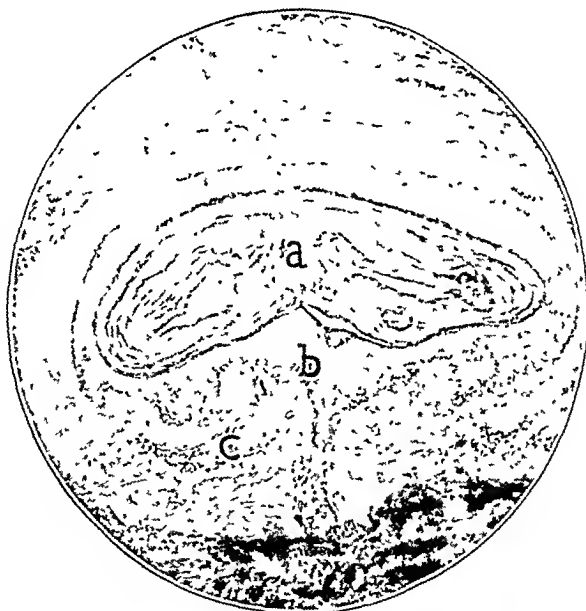


Fig. 9.—Section of a dermal implant at three weeks, showing an epithelial cyst derived from the epidermis of the implant; $\times 100$. The cavity of the cyst, containing horny material, is indicated by *a*, the epithelium lining the cyst by *b* and the papilla beneath the epithelium of the floor of the cyst by *c*.

to the right there was a round hair follicle, cut in transverse section (fig. 10). It showed a similar space between the wall of the follicle and the enclosed hair root, with horny material in it. Another follicle in this section showed the beginning formation of a cyst (fig 11).

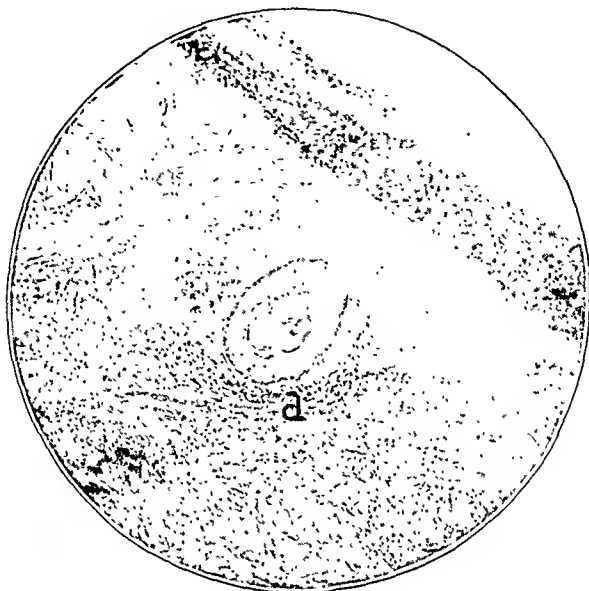


Fig. 10.—Section of a dermal implant at three weeks, showing a surviving hair follicle (*a*) of the implant; $\times 100$.



Fig. 11.—Section of a dermal implant at three weeks, showing a hair follicle in the implant and beginning formation of a microscopic cyst; $\times 100$. The cavity of the cyst, containing centrally placed horny material, is indicated by *a* and the epithelium of the hair follicle lining the cavity of the microscopic cyst by *b*.

Sweat glands were present in this implant, but they showed degenerative changes. They were thinner, stained poorly and were invaded by mononuclear cells (macrophages).

One of the most marked features of this section was the marked response of the connective tissue of the site of implantation. The implant was practically surrounded with young connective tissue, which in places contained many lymphocytes, macrophages and endothelioid cells. In two regions there were definite accumulations of giant cells—near the upper right angle and adjacent to the left margin. Here there was a marked accumulation of granulation tissue with a number of giant cells, and in one area a definitely outlined granulomatous nodule or large oval accumulation of closely packed epithelioid cells and lymphocytes with a fibrous capsule.

In the few areas where adipose tissue was in contact with the lower margin of the implant, the fat cells had been invaded by large mononuclear cells, which

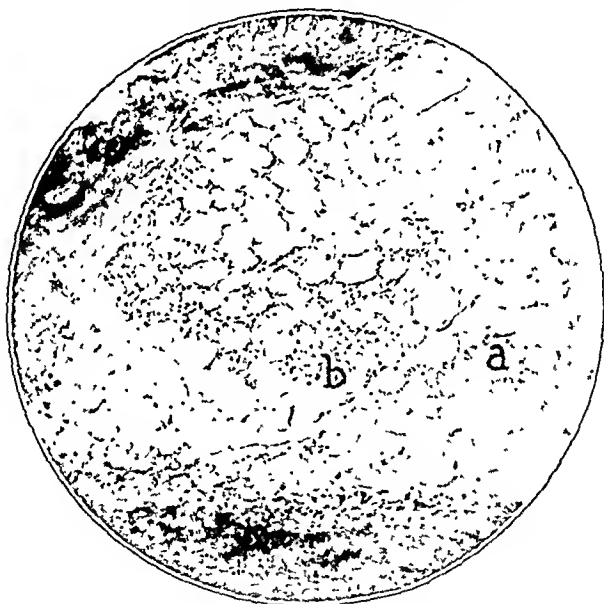


Fig. 12.—Section of a dermal implant at three weeks, showing the subcutaneous fat tissue of the implant in the process of change to tissue of chronic inflammatory type; $\times 100$. The fat cell is indicated by *a* and the area showing replacement by mononuclear cells (macrophages) by *b*.

filled the spaces between the fat droplets, apparently replacing the fat globules and changing the adipose tissue into tissue of the chronic inflammatory type (fig. 12).

The next section represented a considerably later stage of the subcutaneously implanted dermis (fig. 13). It was obtained after two months of implantation. The implant lay at an angle with the overlying skin, its left border in contact with the deeper layers.

Along the slanting upper border of the implant, which was rather clearly defined, there was a sharply defined layer of epithelium bent on itself at the lower border, forming a sharp-angled fish-hook, with the point turned upward toward the overlying skin (fig. 14). In the cavity of the angle could be seen plainly the concentrically arranged layers of the cast-off horny layer, as well as a number of remnants of hair (fig. 15). The roof of the cavity of this partly epithelized

cyst, where epithelium was lacking, was formed from a granulation tissue with a fairly well defined border. It contained numerous lymphocytes, macrophages, epithelioid cells and giant cells. Many of the epithelioid cells and giant cells were markedly vacuolated. There was one large hair fragment embedded in this tissue. This granulation tissue extended to the left above and in contact with the bent epithelial process which formed the epithelized portion of the roof. To the right

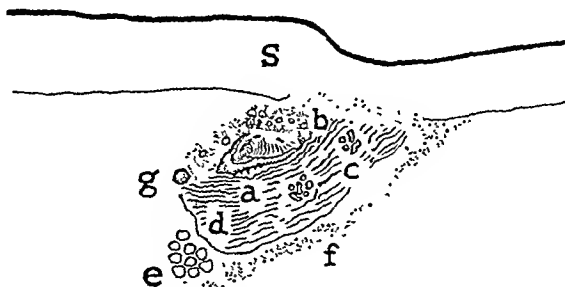


Fig. 13.—Diagram of a dermal implant at two months. *S* indicates the overlying skin of the chest; *a*, a cyst partly lined with epithelium, containing horny material and fragments of hair; *b*, granulation tissue, containing giant cells, forming the roof of the partly lined cyst; *c*, surviving sweat gland tubules; *d*, collagenous fibers of the implant; *e*, fat; *f*, granulation tissue surrounding the implant, and *g*, a granulomatous nodule.

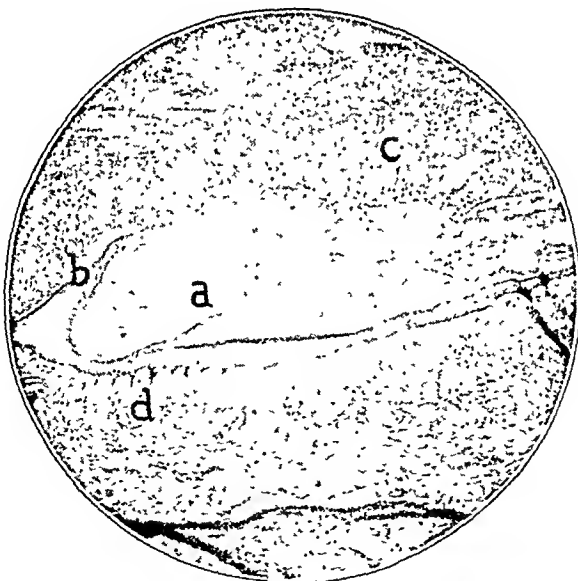


Fig. 14.—Section of a dermal implant at two months, showing an epithelial cyst partly lined with epithelium derived from the epidermis of the implant; $\times 100$. The cavity of the cyst, containing horny material, is indicated by *a*; the epithelium lining the roof of the cyst by *b*; a portion of the roof of the cyst, formed by granulation tissue of the chronic type, containing giant cells, by *c*, and papillae beneath the epithelium of the floor of the cyst by *d*.

it fastened the border of the implant rather firmly to the skin. The other features of this implant were similar to those of the previous sections—persistence of sweat glands with no hair follicles here and a line of granulation tissue extending along the lower border of the implant.

At the left border of the zone of granulation tissue, a little beyond the epithelial margin, there was a small but well defined granulomatous nodule containing the usual elements (figs. 16 and 17).

The two final stages of the implant were observed after seven months and one year of implantation, respectively. They were both characterized by a lack of persistence of the epidermal epithelium, if any were implanted, but showed signs which possibly were to be accounted for by the former presence of epithelium, of the epidermis.

In the section of the implant buried for seven months the implant lay separate from the overlying skin, and at an angle with it (fig. 18). On its upper border



Fig. 15.—Section of a dermal implant at two months, showing the left angle of the epithelial cyst in figure 14 in detail; $\times 370$. The cavity of the cyst, containing concentric layers of horny material, is indicated by *a*; the epithelium lining the cyst at the left angle, apparently turned to form the lining of the cyst, by *b*, and papillae beneath the epithelium of the floor of the cyst by *c*.

there was a series of concentric layers of pink-staining homogeneous material lying in a cavity which had no epithelial lining but was surrounded by granulation tissue above and the dense collagenous fibers of the implant below.

Sweat glands were present but were mostly poorly preserved, with the degenerative changes already described (fig. 19). There were several deeply placed collagenous fibers the same length as the implant (fig. 20).

The granulomatous response of the tissue at the site of implantation was marked. Between the skin and the implant there were two areas which showed a somewhat similar pattern—granulomatous nodules, rather large and oval, containing within their area many densely packed epithelioid cells with numerous

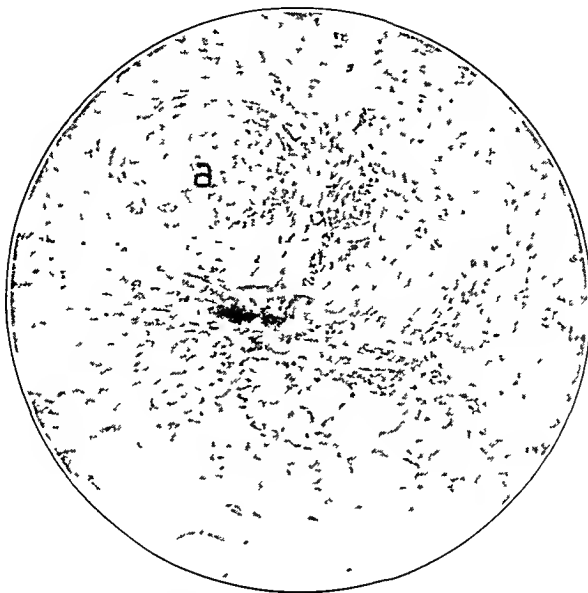


Fig 16—Section of a dermal implant at two months, showing a granulomatous nodule (*a*) with a fibrous capsule; $\times 100$

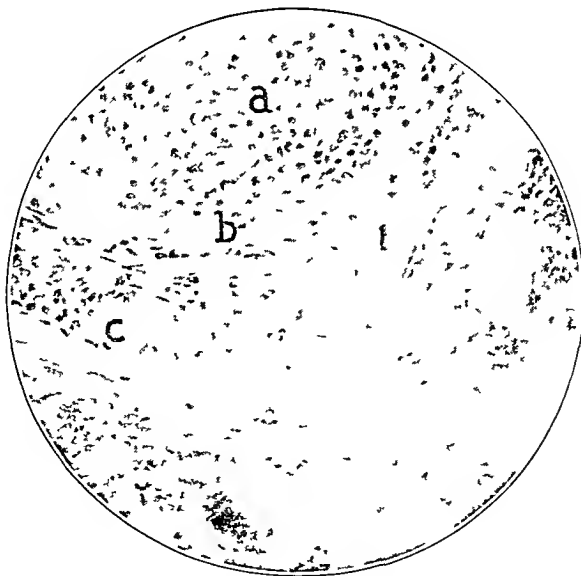


Fig 17—Section of a dermal implant at two months, showing in detail the same cyst pictured in figure 16, $\times 600$ Cells constituting the granulomatous nodule are indicated by *a*, the capsule by *b* and a giant cell, adjacent to the area of the granuloma, by *c*

giant cells. Within each of these areas of microscopic size were small angular refractive bodies, those in the area to the right being more definitely recognizable as hair sections and those in the area to the left, which were more angular, as perhaps remnants of hairs. The bodies in both areas were brownish.

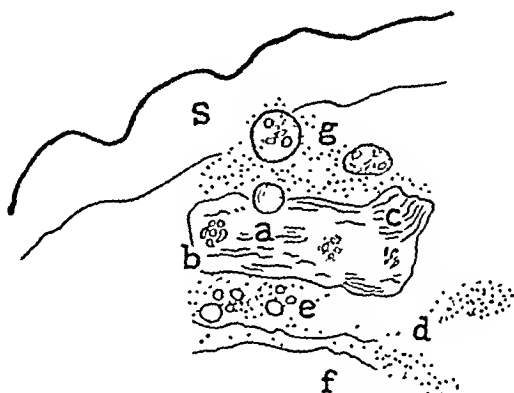


Fig. 18.—Diagram of a dermal implant at seven months. *S* indicates the overlying skin of the chest; *a*, a cyst containing horny material, without an epithelial lining; *b*, sweat gland tubules, showing partial degeneration; *c*, collagenous fibers of the implant; *d*, granulation tissue surrounding the implant; *e*, cavities in the granulation tissue surrounding the implant (granulomas?); *f*, deeply placed collagenous fibers of the implant, and *g*, granulomatous nodules.



Fig. 19.—Section of a dermal implant at seven months, showing partial degeneration of the sweat gland tubules; $\times 100$. The sweat gland tubules, showing degenerative change, are indicated by *a* and the collagenous fibers of the implant by *b*.

Another feature of this section was the formation of large round cavities in the granulation tissue underlying the dermis. As they were surrounded by macro-

phages and epithelioid cells, they were believed to be similar in structure to the aforementioned granulomatous nodules, but with their contents lost in preparation.

The final section, obtained after one year's implantation, showed the implant in contact with the overlying skin along its whole upper border (fig. 21). Nevertheless, the probable upper margin of the implant could be recognized by comparing the depths of tissue in the region of the implant with that at both sides and by observing the newly formed layers of fibrous tissue. Along what appeared to have been the upper margin of the implant, there was a fairly large transversely elongate oval cavity, containing somewhat concentrically arranged horny material. There was no definite epithelial lining (fig. 22). The roof was formed by what was apparently a late or fibrous stage of granulation tissue, with a few small giant cells and some remnants of hairs. The floor was formed by the dense fibers

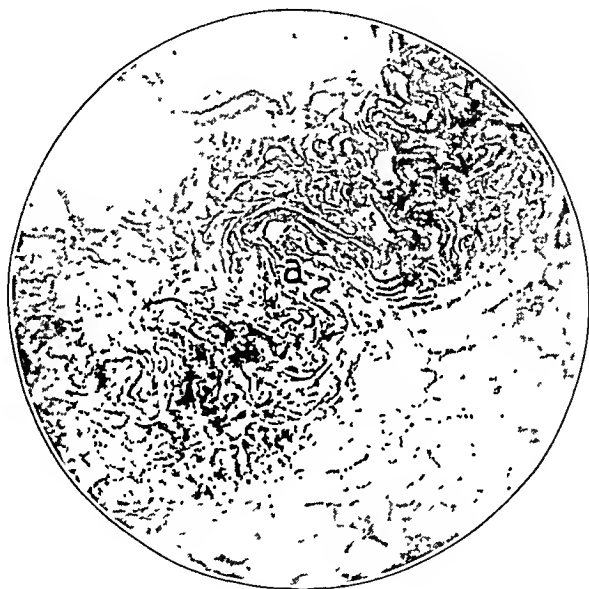


Fig. 20.—Section of a dermal implant at seven months, showing deep connective tissue fibers of the implant; $\times 100$. The connective tissue fibers, showing waving and consequent longitudinal shrinkage of the implant, are indicated by α .

of the implant. No epidermal epithelium was seen in this implant. Sweat glands were present, but were altered in shape and showed degenerative changes in the epithelium of the tubules (fig. 23). No hair follicles were seen. In this, as in all the five preceding sections except the first, no sebaceous glands were found. The implant appeared rather densely adherent to the overlying skin, along its upper border. There was no definite evidence of granulation tissue except in the portion of the section overlying the implant in the region of the scar, where it was in a late stage. Beneath the implant there was rather normal adipose tissue.

COMMENT

From the sections described here it seems apparent that the epidermal tissue of the implanted dermal graft, although supposedly

removed, tends to survive.¹⁶ Sebaceous glands were noted only in the section of the implant buried for one week, and hair follicles were found only in sections of the implants buried up to three weeks inclusive.

It may be claimed that epithelial tissue in these sections need not have been derived from the implant, since it was already present in

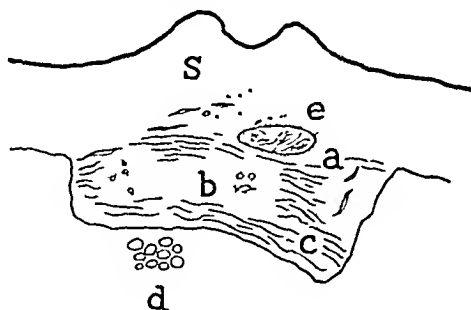


Fig. 21.—Diagram of a dermal implant at one year. *S* indicates the overlying skin of the chest, with which the implant has fused; *a*, a cyst, containing horny material and fragments of hairs; *b*, altered sweat gland tubules; *c*, collagenous fibers of the implant; *d*, fat; *e*, granulation tissue of the roof of the cyst, forming fibrous connective tissue

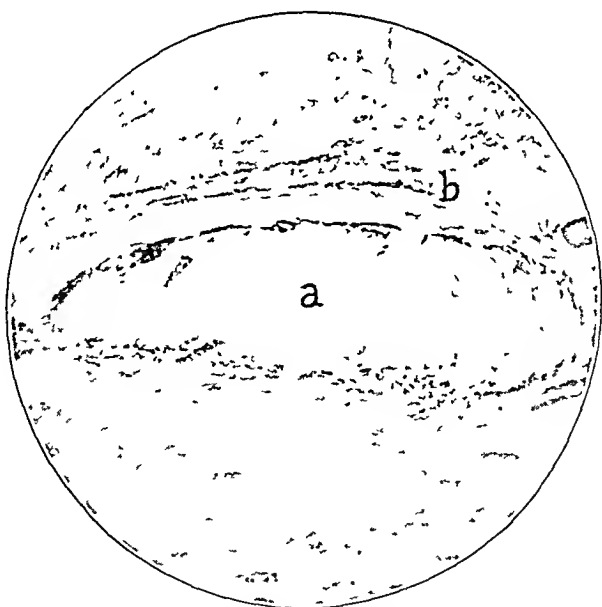


Fig. 22.—Section of a dermal implant at one year, showing a cyst without an epithelial lining; $\times 100$. The cavity of the cyst, containing apparent horny material, is indicated by *a* and the wall of the cyst, showing absence of an epithelial lining, by *b*.

16. In one case of traumatic epithelial cyst of the hand, the original penetrating wound had occurred twelve years previously, and the secondary trauma one month previously (Wien and Caro).

the overlying skin at the time that the implantation occurred. Against this claim the following observation may be brought forward. The position of the epidermal remnant, whether in the form of an epithelial cleft, cyst, island¹⁷ or fish-hook, was invariably found in the zone of the upper margin of the implant, which was exactly the former site of the epidermis of the implant (figs. 1, 6, 8, 13, and 21). The hair follicles were seen in their normal site in the implant (figs. 1 and 8), although many of the fragments of hairs had been displaced. The same normal position was true of the single sebaceous gland (fig. 1, *b*). These facts, in our opinion, should outweigh the more remote possibility that these structures had been displaced from the overlying skin. Since



Fig. 23.—Section of a dermal implant at one year, showing persistent sweat gland tubules and degeneration; $\times 100$. The sweat gland tubules are indicated by *a* and the collagenous fibers of the implant by *b*.

the cysts and other epithelial structures were all of microscopic size and of the same order of magnitude in the later as in the earlier sections, it is evident that they had not increased in size to any appreciable extent. In the case of an epithelial cyst of the palmar surface of the hand, which is traumatic in origin and subject to further trauma, it is noteworthy that such secondary trauma is mentioned as preceding the increase in size of the cyst to clinically appreciable dimensions. It may be that the site chosen for these implants is responsible for the lack of clinically demonstrable cysts. The site of the chest is

17. Zimches, in his implantation experiments with epithelium in dogs' muscles, at times obtained epithelial cysts and at other times solid islands of epithelium.

undoubtedly protected from trauma in comparison with the palmar surface of the hand. It is well to bear in mind the different functions of the skin due to the wear and tear of manual friction and the correspondingly greater thickness of the horny layer of the skin of the palmar surface.

However, in our experiments there was no evidence of deterioration of the buried epithelial remnants, with the possible exception of the two specimens of the longest duration, in which small cystlike cavities occurred without an epithelial lining (fig. 22). This evidence is speculative, since we do not know that these cavities were originally lined by epithelial tissue. At least the appearance of the earlier sections was normal as far as the epidermal cysts are concerned. The hair follicles, present only in the earlier sections (up to three weeks inclusive), appeared to be gradually developing into round epithelial cysts of microscopic size. The hairs, often displaced, were found in larger or smaller fragments both in the cavity of the cyst and scattered through the granulation tissue, especially in the centers of granulomatous nodules and within giant cells (fig. 24). Their demonstration was made easier by the use of polarized light, to which the displaced fragments, just as the normally placed intrafollicular hairs, gave a special rotation and diffraction (fig. 24). It is suggested that the granulomatous reaction is due, at least in part, to these structures which are especially resistant to solution and absorption.¹⁵

The changes in the sweat glands were much more marked in the later sections (figs. 19 and 23). It would seem that they were undergoing slow but continuous replacement by fibrous tissue. The lack of any sebaceous glands in all the sections except the first must be interpreted as a probable indication of their failure to survive, though this is not conclusive, as it is purely negative evidence based on a few specimens. Therefore, while some of the epithelial structures evidently tend to survive, our observations point toward their eventual disappearance.

It is evident that the fate of the true dermal structures as opposed to the epidermal structures is to survive by fusion with the subcutaneous tissue at the site of the implantation (fig. 21). This is mediated by the normal mechanism of inflammation and repair process, being evidently aseptic in all these sections, and the repair process being normal aseptic wound healing, complicated by the presence of foreign material (horny material and hair and lipoids) definitely productive of granulomatous tissue, which often reaches the extent of a heaping up of cells

18. Zimches gave a similar explanation.

of the macrophage type, epithelioid cells and even giant cells into diffuse tissue or nodules of microscopic size (fig. 16).

This extreme form of reaction is characteristic of the "foreign body" reaction and may occur in an epithelioma about the horny substance formed by excessive cornification of an epithelioma nodule (Muir¹⁹).

That this type of reaction is present in the sections obtained after seven months of implantation and almost absent in those obtained after one year of implantation probably means that this difficulty is at last surmounted and the unassimilable material successfully walled off at



Fig. 24.—Section of a dermal implant, showing a foreign body giant cell in granulomatous tissue, and a foreign body derived from hair or horny material; $\times 600$. The giant cell is indicated by *a* and the foreign body by *b* (foreign body demonstrated by use of polarized light).

the expense of increased fibrosis. It is possible, however, as has been suggested by Wien and Caro, that such a granuloma may lead to the formation of a cyst, the walls of the cyst containing granulation tissue with giant cells. They found one such cyst of clinically appreciable size in the hand after cutting by a sharp instrument. (The section is pictured in their article.) Such an explanation would require only the horny layer for the formation of a cyst. Our two final sections may represent microscopic cysts of this type.

19. Muir, Robert. *Textbook of Pathology*, Philadelphia, J. B. Lippincott Company, 1924, p. 111.

CONCLUSIONS

The dermal graft (with epidermis apparently removed) when taken from the skin of the abdomen as a free auto-graft and inserted beneath the skin of the chest remained in place and fused with the surrounding connective tissue.

In the majority of sections, in spite of attempted complete removal of the epidermis, some epidermis remained. This remaining epidermis formed closed cyst cavities of microscopic size, containing horny material and fragments of hairs.

In the later sections (seven months and one year) horny material was seen in the cavities of microscopic size surrounded by granulation tissue without epithelial lining.

Sebaceous glands were noted only in the implants of one week's duration.

Hair follicles were observed only in the implants buried up to three weeks, inclusive.

Sweat glands were seen in all sections, but in later sections they were in the process of degeneration and fibrous replacement.

Granulation tissue surrounding the implant was of the chronic inflammatory type containing lymphocytes, macrophages, epithelioid cells and often giant cells, in some cases with the formation of granulomatous nodules.

In the granulomatous tissue surrounding the implant, at times within the implant, bodies were observed within the giant cells and nodules. These bodies resembled hairs and fragments of hairs.

REPAIR OF INDUCED BONE DEFECTS

CELLULAR CHANGES WHICH TAKE PLACE WITHIN THE FIRST FORTY-EIGHT HOURS

GEORGE WAGONER, M.D
PHILADELPHIA

Much excellent investigative work has been done in an attempt to determine the processes involved in the healing of bone injuries. Practically none of the reported data deal with those cellular changes which take place within the first forty-eight hours after the creation of the bone defect.

In this paper are given the results of experiments designed to determine the early cellular responses to trauma to the bone.

The plan followed in studying the processes of bone repair aims to evaluate the relative function and importance of the periosteum, cortex and marrow.

Investigation was confined to the repair of induced defects of the midportion of the diaphysis of a typical long bone, the tibia. The white rat was used as it is the laboratory animal which has been most frequently used by other investigators and hence concerning which there exist the most varied and exact data. The animals were raised and maintained on a diet adequate in caloric, mineral and vitamin content.

In order to control the influence, if any, of sex on the healing of bone defects, males and females were used in equal numbers. The age of the animal was considered of prime importance in determining the reparative response to trauma. In consequence, the various experiments were performed on a series of young animals and on an equal number of young mature animals.

The experiments were subdivided into three main groups:

1. Partial defect of tibial diaphysis (extending through the periosteum and the outer portion of the cortex)

(a) Young animals

(b) Mature animals

Aided by grant from the Faculty Research Committee.

Accepted as a thesis in qualifying for membership in the American Orthopaedic Association.

From the Laboratory of Orthopaedic Research and the Department of Pathology, University of Pennsylvania.

2. Hemisection of tibial diaphysis (extending through the periosteum, a portion of the cortex and into the medullary cavity)

(a) Young animals

(b) Mature animals

3. Complete section of tibial diaphysis

(a) Young animals

(b) Mature animals

(The data for groups 1a, 1b and 2a have been compiled and will be submitted for publication. Group 2b is considered in this paper.)

HEMISECTION OF THE MIDPORTION OF THE DIAPHYSIAL CORTEX (TIBIA) OF MATURE ANIMALS (2b)

MATERIAL AND TECHNIC

White rats of the Wistar Institute strain, of both sexes, varying from 190 to 260 Gm. in weight, were used. They were raised and maintained on a full maintenance diet.

After the induction of complete general anesthesia by the inhalation of ether, both hindlegs were thoroughly cleansed with 70 per cent alcohol.

Over either the crest or the anteromedial surface of each tibia, under aseptic precautions, a small linear incision was made through the skin and subcutaneous

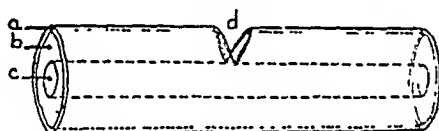


Fig. 1—Diagram of the type of defect (hemisection) made in the tibial diaphysis: *a*, periosteum; *b*, cortex; *c*, medullary cavity, and *d*, defect.

tissues. Hemostasis was employed. The periosteum was exposed in an area devoid of large blood vessels, and a small, specially constructed osteotome was placed in contact with it. The osteotome was driven through the periosteum and the cortex into the medullary cavity by a blow from a small mallet. Care was taken not to induce complete fracture of the bone. The wounds were closed by interrupted sutures of fine silk. Both tibias of each animal were treated in the foregoing manner.

The animals were permitted to recover from the anesthetic and were then killed by inhalation of ether one, two, four, six, eight, twelve, sixteen, twenty, twenty-four, thirty, thirty-six, forty-two and forty-eight hours after operation.

Both lower legs of each animal were amputated at the knee, and from each the foot was removed at the ankle joint.

The legs were fixed in a dilute solution of formaldehyde U. S. P. (4 per cent) or in Muller's solution.

Pyroxylin sections of each tibia were made in accordance with the technic described in a former publication.¹

1. Wagoner, George. The Technique of Preparing and Staining Large Bone Sections for Histological Study, *J Bone & Joint Surg.* 13:325-328, 1931.

Serial sections were cut through practically the entire defect of each tibia. The sections were stained with Hansen and Bock's iron hematoxylin.² The properties of the stain made it possible to study the bone in relation to the presence or absence of calcium. The sections were examined under the microscope with objectives of various powers, including the oil immersion.

HISTOLOGIC EXAMINATION

SERIES 501.—*Animal killed one hour after operation.*

A defect had been made in the midportion of the diaphysis of the tibia extending through the periosteum and cortex into the medullary cavity.

For a considerable distance on either side of the defect the periosteum was separated from the cortex, while the muscular fibers adherent to the periosteum were torn either completely or in part from their periosteal attachment. In the vicinity of the defect, the zone of uncalcified new bone lying immediately beneath the periosteum was stripped from the cortex so that the outer limit of the cortex was marked by the most recently formed cement line.

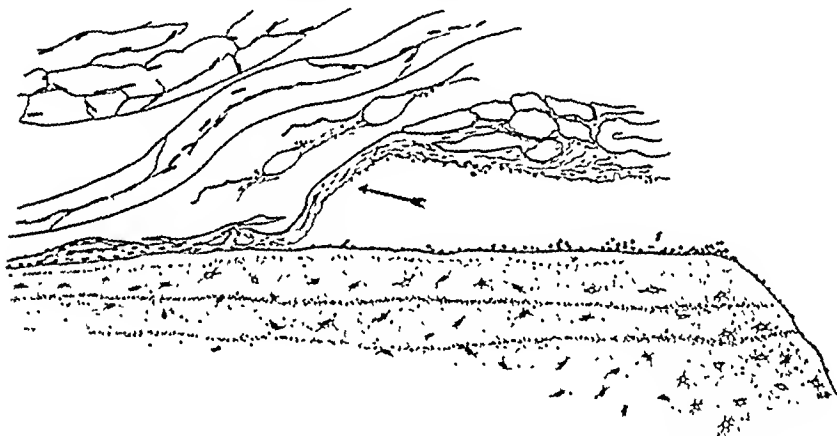


Fig. 2 (specimen 501).—Composite drawing made from study of numerous sections of a one hour defect, designed to illustrate stripping of the periosteum from the cortex in the neighborhood of the defect.

Immediately in front of and occupying the mouth of the defect were numerous muscle fibers. These were edematous and presented the typical appearance of cloudy swelling. Their cross-striations were absent through the greater portion of the tissue but remained present in a small portion of it. When present, the striations were vague and indistinct.

There was a small amount of fibrin in the outer portions of the defect and more particularly in its orifice.

Driven into the defect were many spicules of bone, occasional muscle fibers and at times a hair or two. Hemorrhage bound these structures together and completely filled the interstices of the defect. The amount of hemorrhage was not excessive and was only sufficient to fill the defect without piling the erythrocytes one on another. The muscle fibers present within the defect were not as edematous as those occupying the orifice. Their cross-striations were absent. The osteo-

2. The data contained in this paper were obtained from the study of approximately 2,500 stained and mounted sections cut from over 60 tibias.

cytes of the spicules of bone in the defect were occasionally degenerated and in some cases absent. In a number of other instances there was apparently no change in the osteocytes of these spicules

The fibrillar (lamellar) structure of the cortical bone was beautifully illustrated by the occurrence of many bone "fibers," which closely resembled the strands or fibers of a rope. The cement substance which normally binds bone fibers together had given way before the impact of the osteotome, and the cut margins, instead of being sharply sheared, presented a frayed appearance.

It is of special note that the osteocytes of the outer cortical zone in the vicinity of the cut edges had undergone lysis. The lacunae were devoid of nuclei, and such cytoplasm as remained was faintly staining and of a granular texture

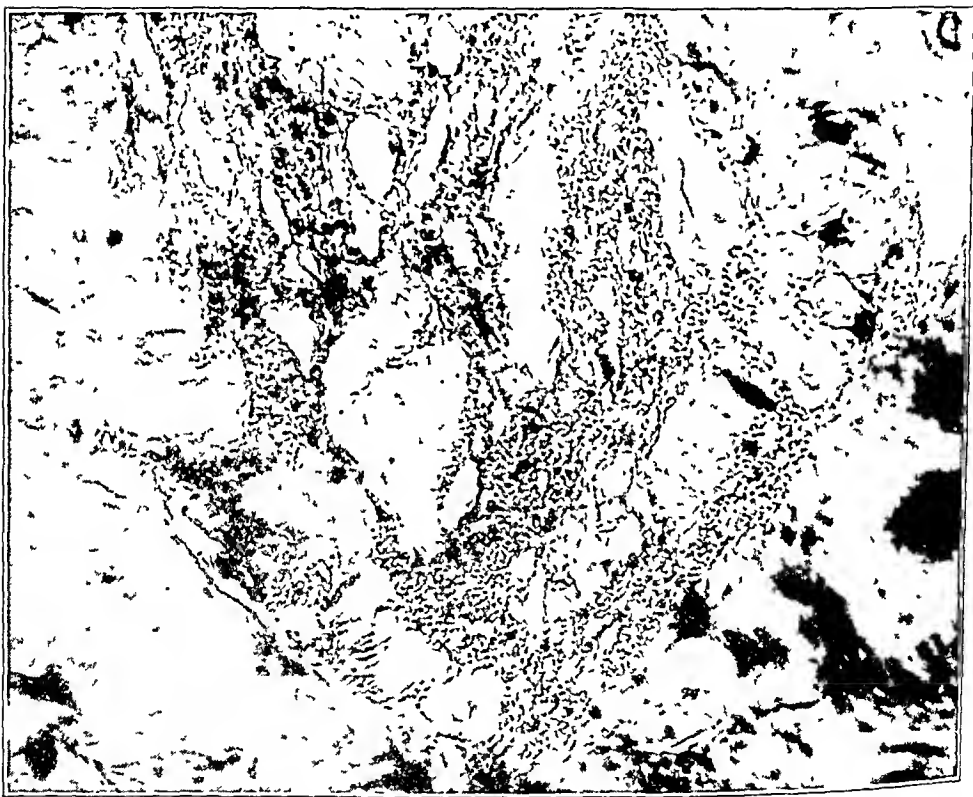


Fig 3 (specimen 501)—Photomicrograph showing fresh hemorrhage into the depths of the defect, $\times 250$, one hour defect. Note the spicules of bone

The canaliculi radiating from these lacunae stained more faintly than did those of the adjacent bone in which the osteocytes showed no evidence of solution

There had been no extrusion of the cellular elements of the marrow into the apex of the defect

SERIES 502—Animal killed two hours after operation.

In this specimen the defect extended through the periosteum and cortex into the myeloid canal and by contrecoup through the opposite cortical wall. The subcutaneous tissues overlying the orifice of the defect were edematous and infiltrated with many polymorphonuclear leukocytes and large and small lymphocytes

The double layer of osteoblasts lining the cortical margin was absent for a considerable distance on each side of the defect. The periosteal nuclei were absent in this same area. The fibers of the periosteum were distended by edema. The zone of uncalcified bone could not be seen.

The defect was filled with hemorrhage which was more dense than in section from the animal killed one hour after operation, and in it were found many lymphocytes and leukocytes. The hemorrhage had infiltrated the small spaces formed by the separation of the lamellae and thus extended into the substance of the cortex on each side of the defect throughout the entire depth of the cut. The lysis of the osteocytes had extended radially through a larger area than in the previous specimen. The cortical bone immediately adjacent to the defect stained more poorly than normally and was developing a granular character. The cut edges were less sharp and irregular. They seemed to be softer than the adjacent bone.

The cellular elements of the medullary cavity had extruded into the apex of the defect and were displacing the hemorrhagic elements. The marrow cavity itself was almost entirely devoid of hemorrhage, and no change could be detected in the composition or in the arrangement of the cellular elements of the marrow in the vicinity of the cut.

SERIES 504.—Animal killed four hours after operation.

The soft tissues, chiefly muscle, overlying the cortex of the bone at the site of the defect were edematous, but to a lesser degree than in the earlier specimens. The fibers and bundles were more closely packed, whereas the areolar tissue between them was less prominent. There was a distinct numerical decrease of infiltrating leukocytes and lymphocytes.

The periosteum in the vicinity of the defect was in closer approximation with the cortex of the bone, and in places was in direct contact with it. The periosteal layer of osteoblasts had approached the mouth of the defect, and there was a resumption of the proliferation of new osseous tissue.

The fibrinous network occupying the orifice of the defect was more dense and was undergoing organization. Particles of muscle previously present had undergone almost complete degeneration. The spicules of bone had lost their cellular character and were in the process of decalcification. Cellular resorption of these spicules was not present. Osteoclasts could not be seen in or near the defect.

There was almost complete disappearance of the erythrocytes, formerly seen in such profusion in the defect. The marrow elements had extruded higher into the defect and were practically replacing the hemorrhage. The interstices in the lower half of the defect were filled in by the marrow elements.

The zone of osteocytic degeneration in the adjacent cortex had increased.

The edges of the cut cortex showed still further absorption and rounding off of their formerly sharp and irregular margins, and for a small distance into the cortex the bone in this area had lost its staining properties to a great degree. A pale pink-staining slightly granular material was invading the defect from the upper surface of the cut edges of the cortical bone. Occasional cells, both polymorphonuclear leukocytes and monocytes, were scattered throughout this pink-staining material.

Those spicules of bone which had been pushed into the marrow cavity were rapidly losing their cellular structure through the death of the contained osteocytes and the obliteration of the canaliculi and cement lines. The spaces between the bone fibers had increased, and the intrusion of the myeloid elements into these spaces had increased. The spicules in the defect had lost to a marked degree the property of absorbing the hematoxylin stain. A definite granularity appeared

throughout the spicules; their margins, losing their sharp, well defined surface, were becoming softly irregular. At one or two points the lodgment of osteoclasts, with resultant lacunar absorption, could be detected. The almost complete absence of osteoclasts with their resorptive lacunae was conspicuous.

With the exception of a slight amount of hemorrhage in the marrow substance in the immediate vicinity of the depressed bone fragments, the cellular marrow presented no apparent abnormalities.

SERIES 512.—*Animal killed twelve hours after operation.*

The edema of the muscle tissues adjacent to the defect was markedly diminished, and, for the most part, the bundles had returned to normal size but continued to be deficient in nuclei. Some of the bundles were undergoing degeneration and absorption (lysis).



Fig. 4 (specimen 512).—Photomicrograph showing progressive resorption of spicules of bone and filling of lamellar interspaces with marrow elements and an absence of osteocytes. Hansen and Bock's iron hematoxylin stain; $\times 180$; twelve hour defect.

The defect was solidly filled with bone chips, cellular elements of the myeloid canal and blood; all were bound together in a strong, well organized mass of interlacing fibrous strands. The hemorrhage was beginning to disappear.

Those bone chips lying in the subcutaneous tissues outside of the defect stained poorly, had lost for the most part their cellular detail and were in the process of absorption (necrosis). Osteoclastic resorption of these fragments was absent.

The presence of marrow elements in the defect and in the spaces created between the bone fibers was more marked than in previous specimens. Evidence of hemorrhage in the deeper portions of the defect was conspicuously lacking. The bone chips lying within the defect had undergone more degeneration than those in the subcutaneous tissues. There did not seem to be an extension of the zone of osteocytic degeneration except perhaps to the area in the external cortical zone immediately beneath the periosteum. The general appearance was that of a fairly firm mass of heterogeneous tissues filling the defect in all parts and bound together and to the adjacent bone by proliferating strands of fibrous tissue.

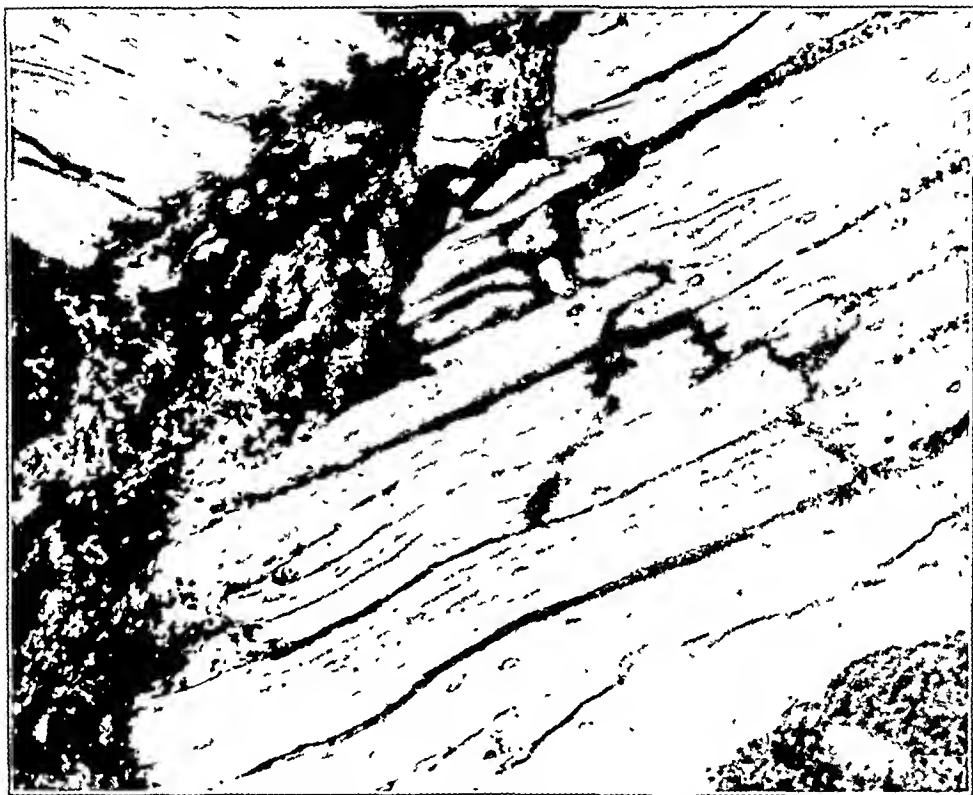


Fig. 5 (specimen 530).—Photomicrograph showing a transverse fracture and longitudinal separation of the cortical lamellae; filling of the interspace, and death and lysis of osteocytes. Hansen and Bock's iron hematoxylin stain, $\times 245$; thirty hour defect.

Monocytes and numerous macrophages were in contact with the bony walls of the defect. Lacunar resorption was present. No osteoclasts were found in the lacunae, the cells therein being chiefly macrophages. Many phagocytosed red blood cells were present in this area.

Within the focal areas of necrosis of cortical bone, adjacent to the myeloid cavity, there was marked invasion of the necrotic tissue by neutrophils.

The monocyte resistance was as yet not great.

No hemosiderin crystals were noted.

The cells found in the outer portion of the defect were those which would arise from blood vessels, namely, nonnucleated red cells, old polymorphonuclears, leukocytes and small round lymphocytes. The majority of these cells were undergoing degeneration.

SERIES 516.—*Animal killed sixteen hours after operation.*

This specimen was distinguished by the greater density of the material filling the defect and by the greater distance with which certain of the cellular elements of the marrow had emerged into the defect. Under oil immersion it was possible to see lacunar resorption in the depths of the defect and in the isolated spicules of bone. The cells engaged in the resorption of bone were not osteoclasts but wandering macrophages derived from the reticulocytes.

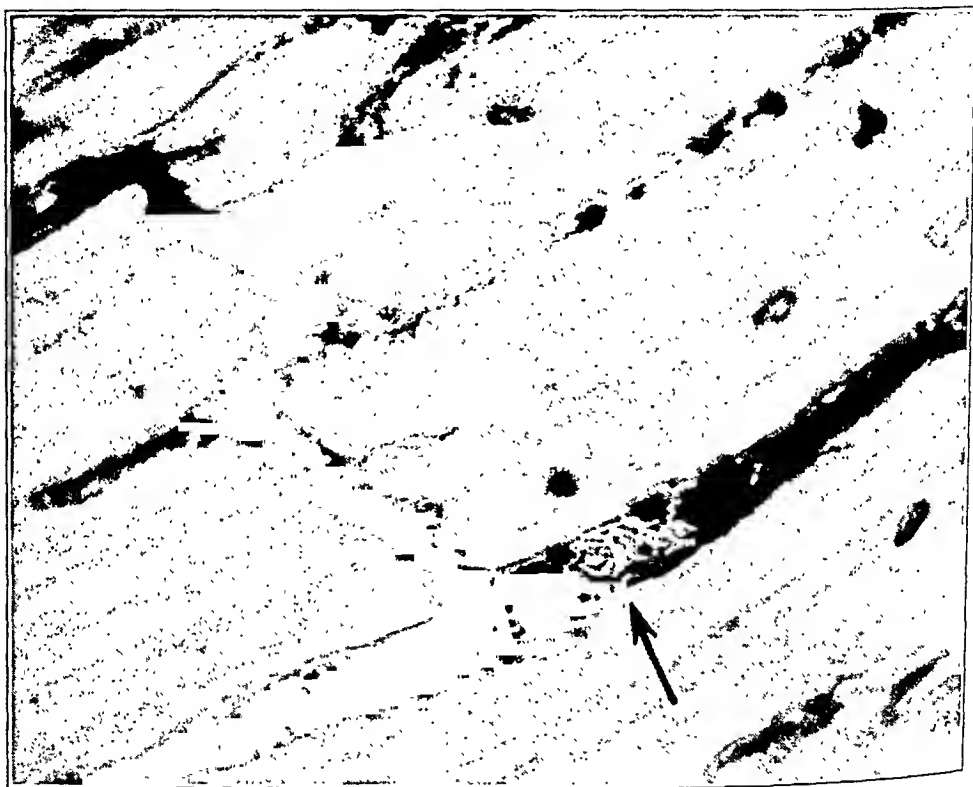


Fig. 6 (specimen 530).—Photomicrograph showing fractured and separated lamellae; an absence of osteocytes, and interspaces packed with cellular myeloid elements. The arrow indicates the giant macrophage. Hansen and Bock's iron hematoxylin stain; $\times 846$; thirty hour defect.

Hemorrhage of the marrow was absent. To one side of the defect and along the endosteal margin was a narrow band of edema. (This may have been an artefact, as in places the endosteal layer of osteoblasts was detached from the surface of the bone.) Edema certainly was present in adjacent areas.

It is of interest that the cells of the bone marrow lying in the defect and those in the canal immediately below the defect had a vertical arrangement—at right angles to the long axis of the bone. This was in contrast with the distant areas of the medulla where the hematopoietic cells had no definite arrangement.

SERIES 520.—*Animal killed twenty hours after operation.*

There was a moderate degree of extra-osseous inflammatory reaction. The cells present were fixed tissue cells and wandering macrophages. Some fibrin was still present. A small amount of necrotic tissue remained, but the work of the scavengers had been well done.

The periosteum was detached in the vicinity of the defect. The orifice of the defect contained a loose skein of fibrin in which were enmeshed numerous migratory cells which may have come either from the blood or from the myeloid cavity. Many of these cells were neutrophils, while an almost equal number were macrophages. Deeper in the defect the fibrin was more dense, but it became less dense as the apex was approached. Necrotic muscle strands and spicules of bone were present. Disintegrating erythrocytes were present in small numbers. At the apex of the defect hematopoietic tissue formed the main contents together with a small amount of fibrin and a few erythrocytes. Similar contents filled the clefts between the frayed cortical lamellae.

Lacunar resorption was not as apparent in this specimen as in the two earlier ones.

The medullary contents were normal; neither hemorrhage nor deposits of hemosiderin were noted.

SERIES 524.—*Animal killed twenty-four hours after operation.*

The orifice of the defect was completely bridged over by the extra-osseous tissue. The outermost layer was comprised of muscle bundles, which were edematous. The bundles were separated, and in the interstices deposits of fibrin were present. In the meshes of the fibrin network were many wandering cells, chiefly lymphocytes and polymorphonuclear leukocytes. Some of the muscle fibers were fragmented, and the fragments were necrotic. As the mouth of the defect was approached, the deposit of fibrin became more dense. It had completely replaced the areolar tissue. It was arranged in dense whorls and heavy strands throughout which were many wandering cells. No bacteria were seen. Few erythrocytes were present.

The periosteum, the subperiosteal osteoblasts and the layer of uncalcified bone were present on each side of the defect up to the margins of the cleft. These gave the appearance of having been detached but reunited to the cortical bone.

The material filling the defect was in contact with its sloping sides to which it was firmly united. The cortical margins of the defect were granular and poorly staining and showed marked erosion and softening.

The osteocytes in the vicinity of the defect were for the most part absent, and their lacunae were filled with faintly-staining granular material; the canaliculi were indistinct.

The spicules of bone in the defect were in various stages of lysis, those at the bottom being more necrotic than those elsewhere.

Myeloid elements occupied the lower third of the defect. Practically no hemorrhage was present in the defect, and no hemosiderin crystals could be seen.

In the spaces formed by the fraying of the cortical lamellae, erythrocytes and myeloid macrophages were found. The adjacent bone tissue was markedly necrotic. Lacunar resorption by the macrophages was present but not in sufficient degree to account for the amount of bone necrosis which was present in and about the defect.

The contents of the myeloid cavity presented no abnormality except for a possible condensation of the cellular elements immediately below the apex of the defect.

SERIES 530.—*Animal killed thirty hours after operation.*

The orifice of the defect was completely closed, and over it the periosteum had reformed. There were, however, no layers of osteoblasts in the immediate vicinity of the defect.

The contents of the defect were less cellular than those of the previous specimens. The fibrin was compact and beginning to undergo organization. There was some fibroblastic proliferation within the marrow tissue of the defect.

Within the medullary cavity immediately below the end of the cortical defect there were grouped along the opposite cortical wall and for a short distance into the cavity a large number of marrow giant cells, megakaryocytes and macrophages. As the apex of the defect was approached it was seen that the major portion of



Fig. 7 (specimen 530).—Photomicrograph illustrating the breaking of the cortex into strands and the zones of osteocytic degeneration. The upward extension of the marrow elements into the defect is shown together with the organization of the contents at the orifice of the defect. Hansen and Bock's iron hematoxylin stain; $\times 100$; thirty hour defect

the material extending downward from the defect was without structure and that it consisted almost entirely of cellular debris and irregular granular masses which were in the process of fusion. Scattered in clumps throughout this material were numerous giant cells and other scavengers. Extending further upward into the defect the material filling it was more acellular and structureless than that in the vicinity of the medullary cavity. The upper third of the defect, however, was filled with newly extravasated red blood cells, together with occasional polymorphonuclear leukocytes and lymphocytes.

As the interstices between the bone fibers were examined, it was found that their contents closely resembled the contents of the defect in its lowermost portion, except for the fact that degeneration of the cellular contents had not proceeded so far. It was possible to identify the various phagocytic marrow cells lying therein. They were surrounded by products of their digestion. One or two of the interspaces had been filled by red blood cells and gave the appearance of recent secondary hemorrhage. In several of the interspaces evidence of fairly recent vascular hemorrhage was present, and among the clumps of red cells were to be found marrow giant cells busily digesting them. The material filling the defect was in close and intimate approximation to the cortical walls. Large lacuna-



Fig 8 (specimen 530) —Photomicrograph showing the cortical zone adjacent to the defect. Note the piling up of osteoblasts at the outer margin and their approach to the defect, the fibrination of the cortex with separation between the longitudinal lamellae and the filling of the created interspaces with cellular elements, and particularly the absence of all osteocytes, excepting five in the lower right corner Hansen and Bock's iron hematoxylin stain, $\times 315$, thirty hour defect

like bays were found along the margin of the walls, and in a number of these could be seen the remnants of huge phagocytic cells. Nowhere was it seen that the cortical walls of the defect were possessed of sharp edges. These had all been smoothed and rounded off, and there had extended peripherally from the defect a marked degree of decalcification of the adjacent bone.

Such bone varied from a homogeneous, structureless mass to one in which canaliculi and some lamella could be seen. The Howship lacunae in this area, however, were devoid of osteocytes. Their peripheral wall was faintly staining, as were the canaliculi radiating from them.

SERIES 536.—*Animal killed thirty-six hours after operation.*

The defect was overlaid with a mass of extra-osseous tissue, chiefly muscle, the individual fibers of which were somewhat edematous and were separated from one another. Those fibers which had been traumatically fragmented had undergone practically complete necrosis. There was a marked infiltration of neutrophils. These cells occupied the spaces between the muscle fibers and were lodged in the

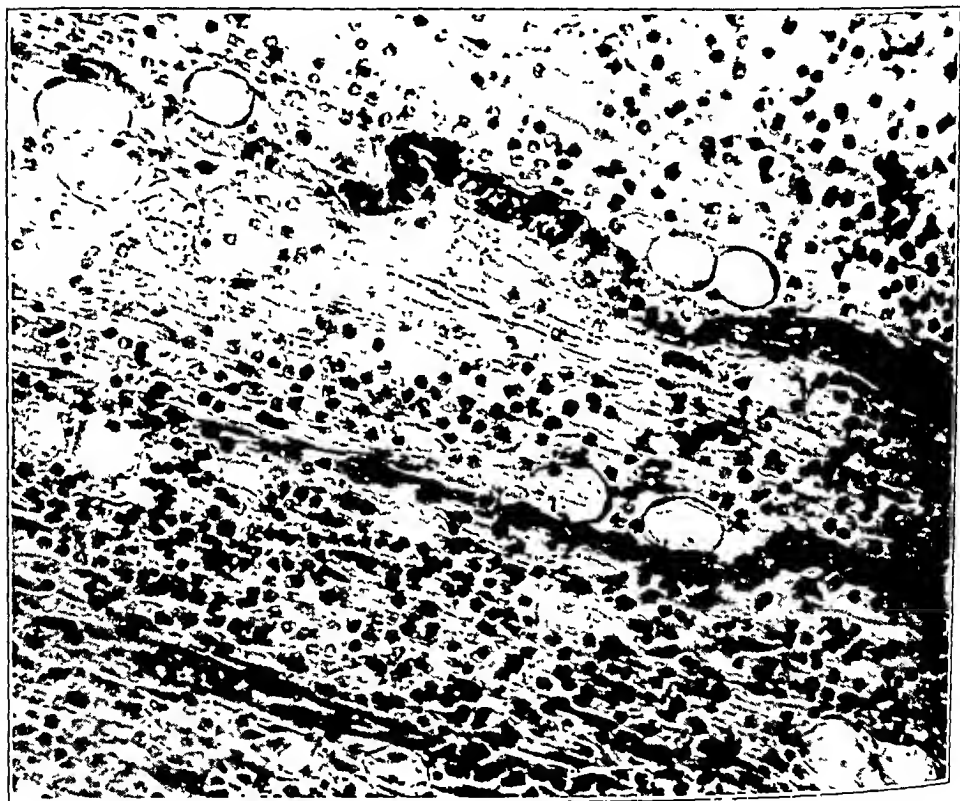


Fig. 9 (specimen 542).—Photomicrograph showing newly formed capillaries in the extra-osseous tissue growing toward the orifice of the defect. Hansen and Bock's iron hematoxylin stain; $\times 277$; forty-two hour defect.

thick network of fibrous tissue, which was rapidly undergoing organization. Scattered throughout the extra-osseous tissues were many spicules of bone of varying size; the smaller ones had undergone almost complete necrosis. The larger ones presented varying degrees of destruction. Although both large and small spicules showed the frequent occurrence of lacunar resorption by macrophages, the number of these cells so engaged seemed too few to be responsible for the amount of resorption presented by the fragments of bone. One obtained the impression that the major portion of the bone lysis was the result of chemical activity rather than of cellular resorption. Very few red cells or their remnants could be seen throughout the extra-osseous tissue. Several depositions of hemosiderin were present.

The periosteum had been loosened from its cortical attachment for some distance on each side of the defect, and the space thus created was filled by a dense fibrous network in which were lodged numerous wandering cells in varying stages of destruction. There was a reappearance of the layer of subperiosteal osteoblasts. These cells were actively engaged in the formation of new bone and were extending toward the margins of the defect. Throughout the cortex beneath the disturbed periosteum and for a considerable distance on each side of the defect there had been destruction of practically all the osteocytes.

The cortical margins of the defect showed more active resorption by macrophages than had been noted in any of the other section specimens studied.

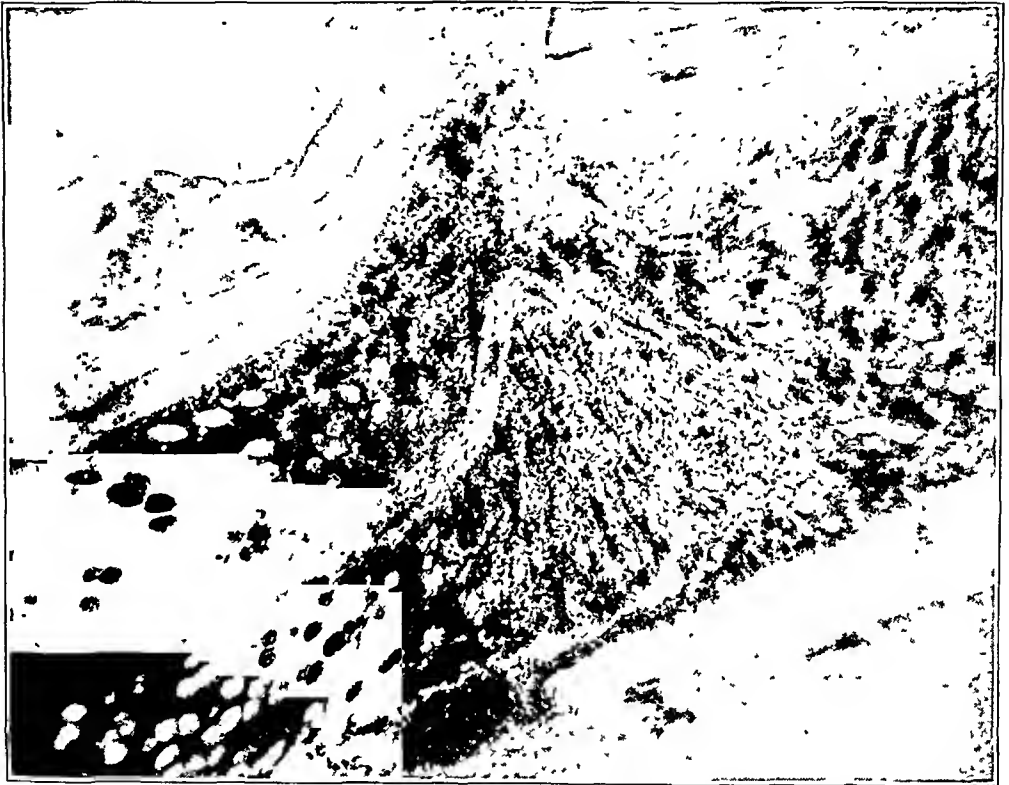


Fig. 10 (specimen 542).—Photomicrograph showing a central marrow capillary bending outward to the base (apex) of the defect. Note the radial alignment of the marrow elements Hansen and Bock's iron hematoxylin stain; $\times 92$; forty-two hour defect.

Although there had been separation of the lamellae of bone along the cement lines, the fimbriation of the cut edges was less marked than previously. There was active invasion of the artificial interspaces between the lamellae by the marrow cells. The lower third of the defect was filled with myeloid cellular material, while the upper two thirds was filled with a dense mass of fibrous tissue undergoing organization, partly resorbed spicules of bone and a rather numerous infiltration of wandering myeloid and blood cells.

SERIES 542—Animal killed forty-two hours after operation.

Throughout the extra-osseous tissue there was a distinct subsidence of the inflammatory reaction and the beginning of definite organization. A marked

ingrowth of new capillaries was present. These new capillaries extended to the margins of the defect but had as yet not invaded the material filling the defect.

The subperiosteal osteoblastic zone showed definite proliferation on each side of the defect and was in close proximity to its margins. The continuity of the periosteum was being restored. The degeneration of the fragmented muscle fibers and of the small spicules of bone lying in the extra-osseous tissues was well advanced, being almost complete for the muscle and partially so in the case of the bone. The orifice of the defect was solidly capped by well organized fibrous tissue in the meshes of which the number of neutrophils had decreased. Practically no red blood cells were now visible in the material

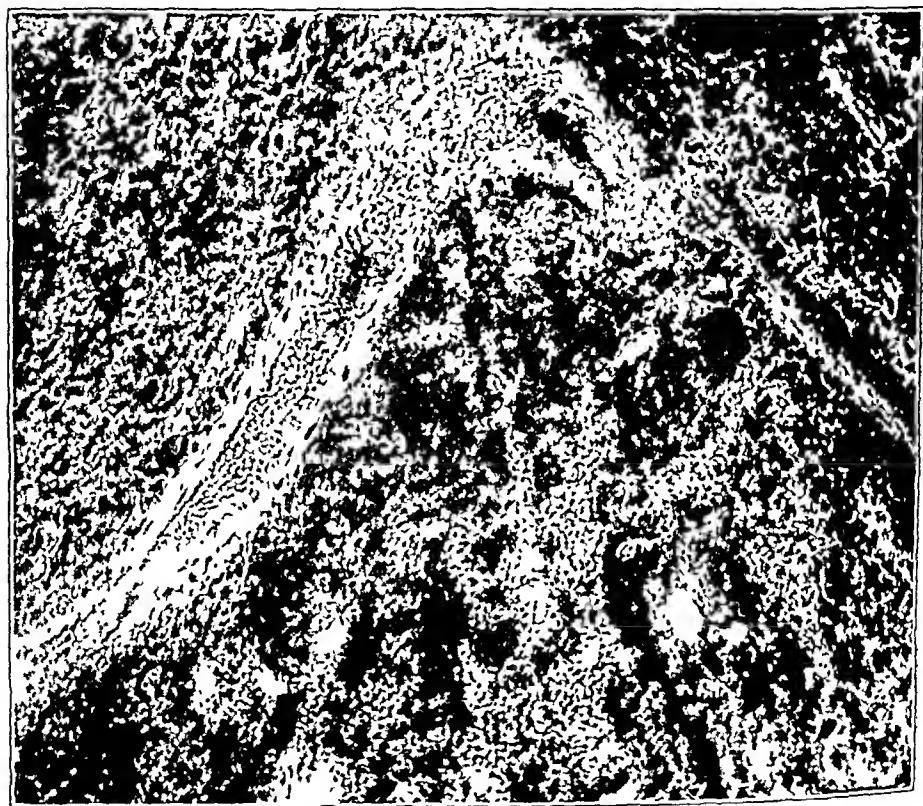


Fig. 11 (specimen 542).—Higher power magnification of the central marrow capillary illustrated in figure 10. Hansen and Bock's iron hematoxylin stain; $\times 277$; forty-two hour defect.

occluding the outer portion of the defect. Occasional deposits of hemosiderin crystals were present in this outer zone. The midportion of the defect contained the remnants of erythrocytes, among which were intermingled the protruding elements of the myeloid canal. The deeper portion of the defect was completely filled with myeloid elements. These also penetrated latterly into the interstices formed by the separation of the lamella. The spicules of bone lying in the defect were rapidly undergoing resorption, and considerable lacunar resorption was being carried out along the margins of the spicules and lamella by the myeloid macrophages. Extending outward from the bottom of the defect were many strands of fibrous tissue, between which were found the granulocytic

cells of the marrow cavity. The zone of osteocytic degeneration, both in the cortex along the margins of the defect and beneath the elevated periosteum, had apparently not increased in size. But it was now quite difficult to recognize the lacunae in which these cells formerly lay, and the canaliculi could not be distinguished.

In the central portion of the myeloid canal in several of the sections was seen a large arteriole running parallel to the long axis of the bone. At the point below the apex of the defect this arteriole was bent in a sharp curve (hairpin curve) toward the apex of the defect. In this same area a radial alignment of the marrow cells was quite apparent. These radiating cell lines had for their center a point in the lower portion of the defect. In several of the



Fig. 12 (specimen 542).—Photomicrograph showing myeloid elements extending into the defect. A capillary is present in the defect. Note also the fraying of the cortex and absence of osteocytes. Hansen and Bock's iron hematoxylin; $\times 240$; forty-two hour defect.

sections there was a small arteriole extending upward in the central portion of the defect for approximately two thirds of its depth. The vessel was probably an offshoot of the large central marrow arteriole arising from the apex of its curve.

SERIES 548.—Animal killed forty-eight hours after operation.

The orifice was completely closed by overlying muscle and areolar tissue. The muscle fibers were not edematous. The cellular infiltration noted in the previous specimens was present in a lesser degree. There was, however, a vast

invasion of actively proliferating fibroblasts and the formation of numerous capillaries. The capillaries had reached the orifice of the defect and were bending downward to penetrate the material occluding it. The periosteum had become reattached to the cortical bone, and at points distant from the defect the osteoblastic layer had reformed and was actively engaged in the formation of new uncalcified bone. It was easily demonstrable that that portion of the periosteum in which reestablishment of osteoblastic activity had taken place was recently separated from the cortex of bone. This was proved by the condition of the extra-osseous tissues, which showed infiltration of cells, the presence of

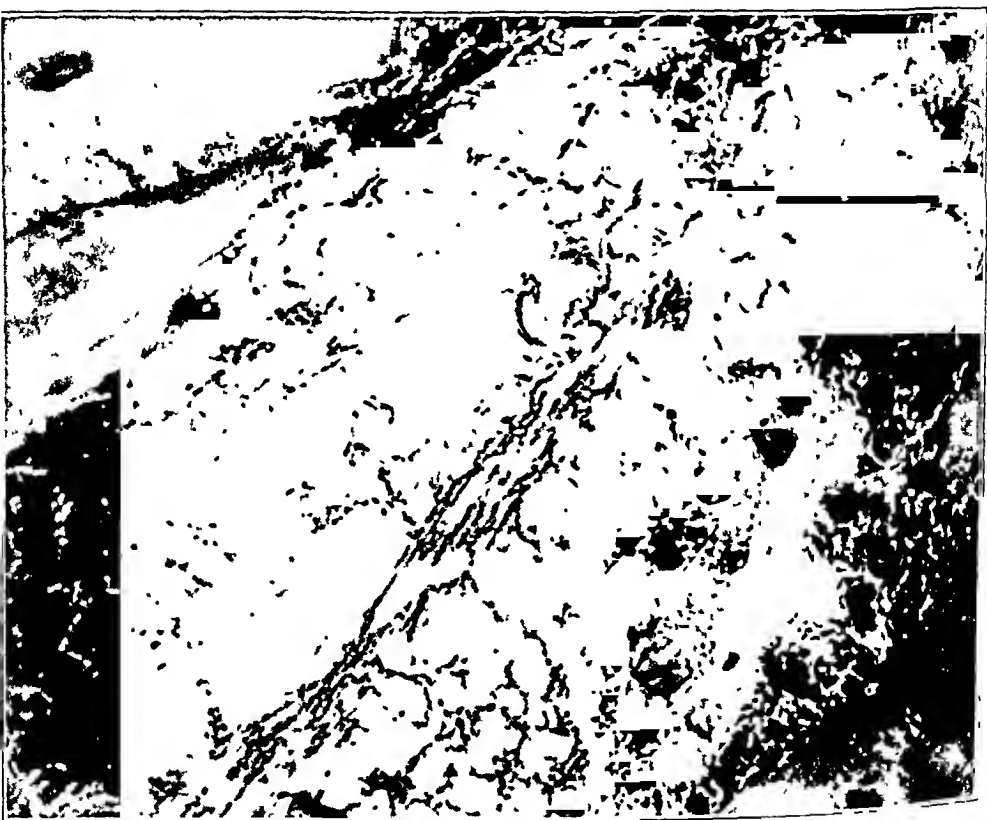


Fig. 13 (specimen 542).—Photomicrograph showing a small capillary from the marrow cavity extending upward into the defect. Note in addition the myeloid elements in the defect and the absence of osteocytes in the lacunae. Hansen and Bock's iron hematoxylin stain; $\times 690$; forty-two hour defect.

granulation tissue and a disturbance of muscle fibers. Furthermore, immediately beneath the portion of the periosteum under discussion the osteocytes lying in the cortex were dead. It was possible, therefore, to state definitely that periosteal reattachment had occurred and that with the reattachment there had been resumption of osteoblastic activity.

The entire defect was solidly filled with dense fibrous tissue undergoing organization. The presence of small islands of pink-staining homogeneous material marked the sites formerly occupied by spicules of bone. In the outer half of the defect it was impossible to note cellular detail, the infiltrating cells having

undergone necrosis. Occasionally in the lower half of the defect isolated giant macrophages could be recognized. The edges of the cortical margins of the defect were frayed and appeared soft and mushy. Some osteoclastic resorption was present but to a lesser degree than in the previous specimens.

SUMMARY

A definite sequence of events followed the making of a defect (hemisection) in the tibial diaphysis of living white rats.

The periosteum was detached from the cortex for some distance on each side of the defect. With this detachment of the periosteum the underlying layer of osteoblasts was destroyed. The zone of newly formed but uncalcified bone in this area was obliterated. Such complete derangement of these structures resulted in interference with the periosteal blood supply to the underlying cortex of bone. In consequence, nutrition of the cortical bone in this area was impaired. Such nutritional impairment was evidenced by necrosis and lysis of the osteocytes. The area of cortical bone so involved increased from hour to hour until the maximum area deriving its nutrition from vessels passing through the deranged periosteal zone was involved. In like manner, the nutrition of the cortex adjacent to the defect was impaired, and its osteocytes were destroyed.

The second interesting fact was the manner in which the cortical bone responded to the trauma incident to the creation of the defect. In adult rats one would expect the cortex to be cut sharply by the osteotome. Instead, it responded in a manner which clearly characterized its structure and physical properties. The cut edges of the defect instead of being sharp showed marked fraying. The fraying corresponded to the longitudinal lamellae of the bone. These lamellae became separated one from the other along their long axes. Separation took place at the cement lines which normally bind the lamellae together. (When bound there is no indication of these lines of weakness.) Furthermore, the intrinsic malleability of the cortical bone was manifested by the manner in which these separated lamellae bent inward before the force of the blow. In some cases this bending equaled an angle of 90 degrees.

Of course, small spicules of bone were broken off and forced into either the extra-osseous tissues or into the defect.

Similarly, fragments of soft tissue, chiefly muscle, were also created. These fragments of muscle, together with the traumatized muscle fibers in the vicinity of the wound, showed marked edema and cloudy swelling at the end of one hour.

The defect was at first filled with erythrocytes as a result of hemorrhage from the several small extra-osseous vessels. Occasional bands of fibrin formed within the first hour. By the second hour there was

present in the extra-osseous tissues and at the mouth of the defect a general invasion of neutrophils. The local edema of the tissues was increased, and marked lysis of the damaged muscle fibers and fragments was well advanced. The hemorrhage within the defect was increased, and the spaces between the separated lamellae were filled with hemorrhagic elements. The zone of osteocytic death had extended by the end of the second hour, not only in that area beneath the stripped periosteum but on each side of the defect. The cut edges of the bone were less sharp, and there was a beginning granularity of the cut margins.

No change could be noted within the myeloid canal.

The third interesting and perhaps most important phase of repair was evidenced by the appearance of myeloid elements within the defect. These elements were first noted in the bone section obtained two hours after operation. They appeared first at the apex of the defect but gradually extended higher into the defect, replacing the hemorrhagic elements which first occupied the breach. It is difficult to determine the manner whereby the myeloid elements entered the defect. Certainly the major portion of the cellular elements found in the defect were those of the migratory type. One cannot say if actual migration, the result of chemotaxis, was the responsible agent. Variation in pressure between the marrow cavity and the osseous defect doubtless existed, and it seems probable that a greater positive pressure, the result of its vascular plexus, existed in the marrow cavity than in the avascular defect. Such difference of pressure would account for the gradual extrusion of the myeloid elements into the defect. The trauma incident to the creation of the defect cannot be responsible for the presence of marrow elements in the defect for two reasons: First, the marrow elements were not present in the earliest sections (one hour after operation), and, second, the lines of force of the trauma would be such as to force the marrow contents away from rather than into the defect.

It is of extreme interest that through practically the entire series of sections osteoclastic resorption of bone was absent. Only occasionally was there found in the large number of sections examined an osteoclast lying within a lacuna of resorption. In the later sections (from the twelfth hour on) cellular resorption of bone was occasionally encountered. The cells so engaged were not true osteoclasts but were giant macrophages arising from the reticulo-endothelial system of the myeloid cavity. Despite the absence of cellular resorption there was marked evidence of bone resolution, as indicated by the progressive rounding off of the edges of cortical bone, by the granularity of the bone along the margins of the defect and by the removal of calcium from the cortical bone, as indicated by its poorer staining properties.

In addition, the spicules of bone lying both within the defect and within the extra-osseous tissue showed progressive evidence of solution. One is forced to the expression of opinion that such bone solution as was most definitely occurring must have been taking place through the process of chemical activity rather than through the medium of individual cell action.

As the age of the defect increased the organization of the material filling the defect proceeded. Its cellular structure became obliterated, and the whole gradually changed into an acellular mass of material firmly bound together and to the walls of the defect by dense strands of fibrous tissue. The periosteum gradually became reattached to the periphery of the cortex; hyperplasia of the osteoblastic layer and the reformation of a new zone of uncalcified bone were progressive changes. In the later sections these peripheral changes were seen to approach the margins of the defect.

In the sections obtained forty-two hours after operation newly formed capillaries were seen in the extra-osseous tissue rapidly growing toward the margins of the defect. In the sections obtained forty-eight hours after operation the capillaries had reached the orifice of the defect and were beginning to turn downward to penetrate the fibrous mass filling the defect. At the same time there was evidence of beginning capillary penetration from the myeloid cavity.

In this paper are described the salient progressive changes which take place within the first forty-eight hours after the creation of a defect in the midportion of the diaphysis of the tibia of the rat, the defect extending through periosteum and cortex into the marrow cavity. The changes were constant, definite and characteristic. No influence of sex on the rate or character of the reparative processes was noted.

CERVICAL RIB ASSOCIATED WITH ANEURYSM OF THE SUBCLAVIAN ARTERY

REPORT OF A CASE AND REVIEW OF THE RECENT LITERATURE

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The occasional presence of cervical ribs in human skeletons was known to Galen, but the first description of a case must be ascribed to Hunauld in 1742. Operative resection of a cervical rib was first carried out by Coote in 1861. Between 1861 and 1895 only eight cases were reported in which operation was performed. Since that time each year has brought increasing numbers of case reports and successful operative results, so that at present cervical rib can hardly be considered a clinical rarity. Of the recognized complications, however, aneurysmal dilatation of the third portion of the subclavian artery is rare. In 1907 Deitmar¹ attempted to collate the literature on this subject and collected reports of five cases, one a doubtful one. Streisler's² monograph on cervical rib in 1913 did not add reports of any new cases despite a complete review of the literature. In 1916 Halsted³ reviewed the reports of seven hundred and sixteen cases of cervical rib, including the available total of clinical, autopsy, and museum material. He reported that aneurysm of the subclavian artery or some degree of dilatation in that vessel was noted in twenty-seven instances. Adson,⁴ whose wealth of experience in the operative treatment of this condition has been unique, stated in 1933 that he had never encountered an example of subclavian aneurysm in association with cervical rib.

From the Department of Surgery, Yale University School of Medicine.

1. Deitmar, cited by Halsted.³

2. Streisler, E.: *Die Halsrippen*, *Ergebn. d. Chir. u. Orthop.* **5**:280, 1913.

3. Halsted, W. S.: *An Experimental Study of Circumscribed Dilatation of an Artery Immediately Distal to a Partially Occluding Band, and Its Bearing on the Dilatation of the Subclavian Artery Observed in Certain Cases of Cervical Rib*, *J. Exper. Med.* **24**:271, 1916.

4. Adson, A. W.: *Surgical Treatment of Cervical Ribs*, *Texas State J. Med.* **28**:739, 1933.

It is the purpose of the present communication to record a new case of subclavian aneurysm in association with cervical rib and to correlate it with cases reported in the literature since Halsted's summary in 1916. There are three of these cases, in two of which the diagnosis was verified by operation.

In May 1922 Moore⁵ reported a case, that of a painter aged 55 whose chief complaint was cough. An incidental and symptomless finding on physical examination was an expansile pulsatile swelling, the size of a walnut, in the left supraclavicular region. Neither thrill nor bruit was present. There was no palpable difference in the radial pulses. Just behind and medial to the pulsatile swelling, a bony protuberance could easily be felt. A roentgenogram showed a cervical rib bilaterally, the right with a free end and the left fused to the first thoracic rib. The Wassermann reaction of the blood was reported as strongly positive. At operation an aneurysm was found in the third portion of the subclavian artery. It appeared as a saccular diverticulum the size of a cherry and sprang from the anterior wall of the vessel. The subclavian artery was otherwise normal. The rib was excised and showed a definite neurovascular groove. The aneurysm was doubly ligated *in situ* without removal. The radial pulse began to reappear on the fourth day.

In October 1931 Billington⁶ described the case of a 42 year old woman who had suffered from pain in the back and in the left shoulder for several years. In May 1930 her physician discovered a tumor above the left clavicle. She began to have pain in the left arm. A difference was noted in the timing of the radial pulses. In June the radial pulse on the left had disappeared, and the arm felt cold. When the patient was admitted to a hospital in November 1930, the fingers of her left hand were cold, numb and pale. A nonpulsatile swelling $2\frac{1}{2}$ inches (6.3 cm.) in length and about the diameter of a walnut was observed above the left clavicle. The left radial pulse was not palpable; there was no motor weakness. The Wassermann reaction of the blood was reported to be negative. A roentgenogram showed a completely developed cervical rib on the right and an incomplete one on the left fused to the first thoracic rib. At operation, through a 4 inch (10 cm.) supraclavicular incision, an aneurysm of the subclavian vessel was exposed. It was adherent to the lower cord of the brachial plexus and was removed by double ligation and section. The cervical rib

5. Moore, C. A.: A Case of Subclavian Aneurysm with Cervical Ribs, *Lancet* 1:1045, 1922.

6. Billington, W.: Excision of Subclavian Aneurysm Associated with Cervical Rib, *Brit. J. Surg.* 19:334, 1931.

associated with this aneurysm was not removed since it did not seem to impinge on the lower cord of the brachial plexus. The excised aneurysmal specimen was found to measure $2\frac{1}{2}$ inches (6.3 cm.) in length and $\frac{3}{4}$ inch (1.9 cm.) in width. The sac was filled with a laminated thrombus showing a minute central channel. There was no microscopic evidence of primary disease in the intima. The muscularis showed some fibrosis, and the internal elastic lamina was duplicated in places and fragmented. The patient made a good postoperative recovery and was completely relieved from pain.

Quinn and Davison⁷ in 1934 described the case of a widow of 75 years who had first noticed a pulsatile swelling on the left side of the neck thirty years previously. One month prior to her observation by the authors she fell on her left shoulder and for the first time began to experience pain, loss of power and paresthesia in the left arm. Examination revealed a pulsatile tumor in the left supraclavicular region approximately 1 inch (2.5 cm.) in diameter. It was tense and elastic, with an expansile pulsation. A systolic thrill and bruit were present. The overlying skin was healthy and freely movable. The brachial and radial pulses were absent on the left. The Wassermann reaction was reported to be negative. Roentgenographic examination showed a well developed cervical rib on the left side and a rudimentary one on the right. Above the left cervical rib the faintly outlined shadow of a mass in the position of the subclavian trunk was present. Owing to the patient's advanced age and relative lack of symptoms, no operation was performed.

REPORT OF A CASE

History.—Mrs. H. L., aged 47, was admitted to the New Haven Hospital on July 24, 1935. Her chief complaint was numbness and weakness of the left arm. For approximately a year the patient had experienced occasional pain in the region of her left shoulder. In March 1935 the pain increased in severity. Her entire left arm began to ache, particularly the inner aspect of the upper part of the arm. She noticed a progressive weakness of this extremity and was soon unable to perform such household duties as sweeping, dishwashing and ironing. If her hands were immersed in cold water her left hand and forearm became "dead white" and numb, but when heat was applied to the extremity it slowly regained its normal appearance and feeling. These attacks of numbness and blanching also occurred spontaneously about once or twice a day and lasted about one hour. More recently the left arm began to feel heavy and lifeless between the attacks. No swelling of the arm or cyanosis was ever observed. The patient was admitted to the hospital

7. Quinn, T. G., and Davison, G.: Left Subclavian Aneurysm in Association with Cervical Rib, *Brit. M. J.* 2:808, 1934.

for hemorrhoidectomy in 1933, and she stated then that she had noted a small pulsatile tumor above the left clavicle. It was symptomless at that time and sometimes seemed to be absent.

The patient's father, paternal uncle and grandfather all died in their forties of a disease of the kidneys and associated complications. The mother died at the age of 46, after an operation for cancer in the region of the neck.

At the age of 7 the patient had measles and scarlet fever followed by dropsy. She had frequently recurring tonsillitis and had influenza during the 1918 pandemic. In 1908 she was thought to have pleurisy. In 1920 she was hospitalized for two weeks because of blood poisoning following an abscess on the right arm. In 1924, at the age of 36, hysterectomy was performed in another hospital. She was told that the ovaries were full of tumor tissue and might become cancerous. The appendix was removed at the same time.

Review of Symptoms.—Severe headaches, lasting from one to several hours, had been noticed for two or three years. Vision was occasionally blurred. At approximately the age of 15 the patient had repeated attacks of epistaxis associated with the spontaneous appearance of dark lumps in the skin along the course of the large superficial veins. After hysterectomy in 1924 this symptom abated. The patient had an illness diagnosed as bronchitis five years before admission, after which a nonproductive cough had been noticed frequently. Menstruation began at 16 and ceased entirely after hysterectomy in 1924.

Physical Examination.—The rectal temperature was 99.8 F.; the pulse rate, 84; the respiratory rate, 18, and the blood pressure 185 systolic and 110 diastolic (right arm). The patient appeared to be a rather poorly nourished and very apprehensive woman of middle age. Her height was 62 inches (157.5 cm.) and her weight 101 pounds (45.8 Kg.). The positive findings were:

The fundi showed arteriolar constriction. Just above the left clavicle and lateral to the border of the sternocleidomastoid muscle was a smoothly rounded mass, 3 by 3 cm., with a definite, expansile pulsation. No thrill could be palpated, but on auscultation a sharp systolic bruit was heard. The skin and subcutaneous tissues were freely movable over the mass, which was much less prominent when the left arm was elevated. The tumor could be displaced slightly by pressure, which caused pain in the arm.

An occasional coarse, crackling râle was heard over the lower lobe of the left lung. The heart was slightly enlarged to percussion, with the maximum apex impulse in the fifth interspace 8 cm. beyond the left sternal border.

A well healed suprapubic midline scar was present.

The fundus uteri was absent. There were no adnexal masses or tenderness to palpation. The anal sphincters were hypertonic.

The arteries of the right arm were slightly tortuous but normally pulsatile. The left arm, however, was definitely cold and pale; the brachial, radial and ulnar pulses could not be felt, although a weak impulse was detected high in the axilla. There was no evidence of localized muscle wasting in the thenar or hypothenar eminences and no demonstrable motor weakness. Thorough sensory examination was everywhere normal except on the volar aspect of the tip of the fifth finger, where there was diminished sensibility to pinprick, heat and cold. All deep reflexes

were equal and active. Oscillometric readings were carried out on the arms with the following results:

Cuff Pressure, Mm.	Right Forearm	Left Forearm
190	0	0
180	$\frac{1}{4}$	0
170	$\frac{1}{2}$	0
160	1	0
150	$1\frac{3}{4}$	0
140	3	0
120	$3\frac{1}{2}$	0
100	4	0
80	$2\frac{1}{2}$	0
60	$1\frac{1}{4}$	0

Cuff Pressure, Mm.	Right Arm	Left Arm
190	$\frac{3}{4}$	0
180	1	0
160	4	0
140	7	$\frac{1}{4}$
120	8	$\frac{1}{2}$
100	$8\frac{1}{2}$	$\frac{1}{2}$
80	$4\frac{1}{2}$	$\frac{1}{2}$
60	$2\frac{1}{2}$	$\frac{1}{2}$

Elevation of the left arm did not change the oscillometric readings.

Studies of the temperature of the skin showed that when the environmental temperature was maintained at 70 F. the surface temperature of the right hand was about 90 F., whereas that of the left hand was 80 F. When the room temperature was raised to 80 F., the skin temperature on the right was stable at 92 F. and on the left it varied from 83 to 87 F. These findings suggested organic occlusion of the vessels on the left rather than pure vasospasm.

Laboratory Examinations.—The Kahn test was negative. The urine contained no albumin, sugar or sediment. Roentgenographic examination on July 25 (fig. 1) revealed a cervical rib on the left, with a faint suggestion of soft tissue swelling near its distal end. The bronchovascular markings were slightly increased, but the pulmonary fields showed no evidence of infiltration. There was thickened apical pleura on the right. The right costophrenic sinus was shallow and showed pleural thickening. The heart was within normal limits as to size and configuration. The aorta was slightly uncoiled and showed some calcification in the knob. There was no evidence of intrathoracic aneurysm. The right transverse process of the seventh cervical vertebra showed a slight prolongation suggesting a rudimentary rib.

Diagnosis.—A diagnosis was made of arteriosclerosis and hypertension, a cervical rib on the left side and an aneurysm of the left subclavian artery.

Operation and Course.—On August 1 operation was performed with the patient under tribromethanol and ethylene anesthesia. The patient's neck was extended and rotated toward the right, and a left supraclavicular incision was made approximately 12 cm. in length, 3 cm. above and parallel to the upper border of the clavicle. The posterior margin of the sternocleidomastoid muscle was freed from its insertion on the clavicle. After transection of the omohyoideus muscle and

the transverse cervical artery, an excellent exposure of the region of the scalenus muscle was obtained. The tip of the cervical rib was identified between the scalenus anticus and the scalenus medius muscle. Lying on it were the subclavian artery and the lower cord of the brachial plexus, definitely distorted in their course. At the point where the cervical rib impinged on the undersurface of the subclavian artery the vessel was approximately 4 mm. in diameter. Immediately beyond this point the vessel dilated into an aneurysmal sac, which was fusiform



Fig. 1.—Roentgenogram of the upper part of the chest, taken on July 25, 1935.

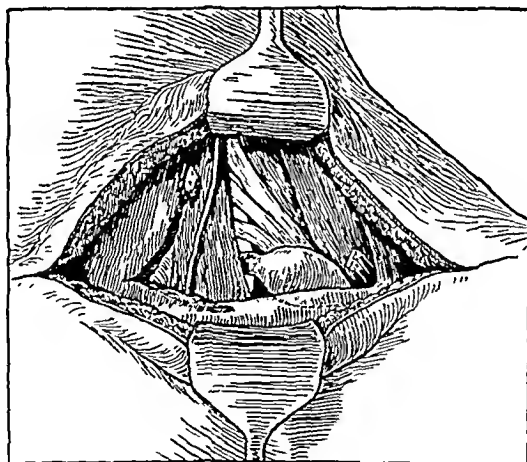


Fig. 2.—Sketch of the operative field (with drapes eliminated).

in outline and measured 2 cm. in its greatest diameter (fig. 2). At the point where the vessel disappeared again under the clavicle it approached a caliber of 8 mm. The aneurysmal sac was slightly but definitely pulsatile. The cervical rib was adherent by dense fibrocartilaginous bands to the upper surface of the underlying first rib. By retracting the brachial plexus upward and outward and the aneurysmal dilatation of the subclavian downward and mediad, the cervical rib was adequately exposed and the distal 4 cm. was rongeured away. After this

procedure the phrenic nerve was isolated from the scalenus anticus muscle, and the latter was severed completely at its insertion on the first dorsal rib. The wound was closed without drainage.

The patient stood the operative procedure well, but on the following day signs of lobar atelectasis involving the lower lobe of the left lung developed. A roentgenogram of the chest taken on August 3 revealed an absence of the left cervical rib except for a small stump at the vertebral end. No pneumothorax was visualized. The left dome of the diaphragm was elevated, and the lower part of the left pulmonary field was definitely opaque. In the lower part of the right pulmonary field there was a slight pneumonic infiltration. The condition in the chest cleared rapidly, and the vital signs were normal again on the fourth post-operative day. The wound healed per primam. During the convalescence there was pain at night in the left elbow and forearm over the distribution of the eighth cervical and the first thoracic nerve. This pain was absent during the day and had disappeared at the time of discharge on August 8.

A follow-up examination on August 17 revealed a definite though slight radial pulsation to be present at the left wrist. Both hands were of normal color and felt to have approximately the same temperature. The patient noticed a distinct improvement in subjective sensation, and she was able to wash dishes for the first time since the previous spring. The operative site was well healed.

She was observed again on October 16. During the first week of the month she had paresthesia in the left arm, which cleared without treatment. Numbness and pain had entirely disappeared. She had gained 2 pounds (0.9 Kg.) in weight. She was using the arm for various kinds of housework, such as sweeping and ironing, without undue fatigue. The palpable aneurysm had not changed appreciably in size.

Oscillometric studies of the left arm were made on that date:

Cuff Pressure, Mm.	Forearm	Arm
190	0	$\frac{1}{2}$
180	$\frac{1}{2}$	$1\frac{1}{4}$
160	1	$1\frac{1}{2}$
140	$\frac{3}{4}$	$1\frac{1}{2}$
120	$\frac{1}{2}$	$1\frac{1}{4}$
100	$\frac{1}{2}$	$\frac{3}{4}$
80	$\frac{1}{2}$	$\frac{1}{2}$
60	$\frac{1}{4}$	$\frac{1}{2}$
40	0	$\frac{1}{4}$

Temperature studies showed the skin of the fingers to vary bilaterally from 85 to 87 F. in an environmental temperature of 70 F.

COMMENT

In regard to diagnosis, Keen⁸ wrote in 1907:

Usually the pulsation is visible as well as palpable, and is marked. It is occasionally noted that it is "expansile." Bruit and thrill, one or both, are often present, the latter less frequently than the former. The bruit, however, is not propagated. Neither the thrill nor the bruit seem to be of the true aneurysmal character.

8. Keen, W. W.: The Symptomatology, Diagnosis and Surgical Treatment of Cervical Ribs, *Am. J. M. Sc.* **133**:173, 1907.

He quoted a letter from Paget to Professor Turner warning against confusion of an abnormally high and easily palpable subclavian artery with a true aneurysm of the same vessel. Murphy,⁹ after finding at operation only a slight cylindric dilatation of the subclavian vessel in a patient with cervical rib who presented clinically a large pulsatile supraclavicular swelling, concluded that a diagnosis of aneurysm in this situation was rarely warranted without operative verification.

There is no agreement in the literature as to the proper mode of therapy when aneurysm of the subclavian artery is associated with cervical rib. A study of case records indicates that this type of aneurysm does not tend to increase in size with secondary manifestations of pressure or danger of rupture. If anything, the contrary is true, for occasionally spontaneous thrombosis has been noted as in the case of Billington.⁶ The simple application of a pressure bandage to the supraclavicular region has resulted in the clinical disappearance of the tumor in certain cases.² According to Keen, in no case prior to 1907 had the vessel been ligated, which he considered wise conservatism. The relatively benign nature of these lesions is well illustrated by the patient of Quinn and Davison; in her case a swelling in the neck had been noticed for thirty years, although no symptoms appeared until a fall one month before the time of diagnosis. It would seem, therefore, that surgical removal of such aneurysms should be advised not as a routine but only for cogent indications. The adherence of the aneurysmal dilatation to the lower cord of the brachial plexus, as in the case of Billington, may be considered a proper indication. It is possible, however, that scalenotomy, as advised by Adson,¹⁰ with or without partial resection of the cervical rib, would have given adequate relief in this case.

The question arises whether local pathologic change in the third portion of the subclavian artery may affect the circulation of the upper extremity unfavorably by reflex effects on the peripheral arteries. Influenced by Leriche's hypothesis that a local pathologic process in an artery may create a focus of hyperexcitability and thus a point of origin for vasoconstrictor impulses mediated through the periarterial sympathetics, Langeron¹¹ expressed the belief that simple resection of the cervical rib did not suffice to relieve symptoms referable to vaso-spasm when secondary changes had already occurred in the subclavian artery

9. Murphy, J. B.: A Case of Cervical Rib with Symptoms Resembling Subclavian Aneurysm, *Ann. Surg.* **41**:399, 1905.

10. Adson, A. W., and Coffey, J. R.: Cervical Rib: A Method of Anterior Approach for Relief of Symptoms by Division of the Scalenus Anticus, *Ann. Surg.* **85**:839, 1927.

11. Langeron, L.: Sur les manifestations vasculaires liées à la présence de côtes cervicales, *Paris méd.* **2**:43, 1933.

at the point of impingement of the cervical rib. Therefore, in two patients with cervical rib who presented evidences of vascular occlusion of the arm and at operation showed degenerative and thrombotic changes in the subclavian vessel in its third portion, he carried out local resection of the pathologic portions of the artery, in one case combined with resection of the cervical rib. Both patients showed lasting relief from vasoconstrictor crises and healing of trophic disturbances. It might be thought that aneurysmal dilatation alone could act as a focus of irritation and should therefore be excised when scalenotomy or resection of the rib is performed. However, irritation of the sympathetic and sensory fibers present in the lower cord of the brachial plexus by an impinging cervical rib is to us a more satisfactory explanation of the vasospastic phenomena. Newell¹² found microscopic evidences of degeneration in the lower cord of the brachial plexus of a patient with cervical rib. Vasoconstrictor crises, peripheral thromboses and even gangrene of the finger-tips have been observed in cases in which the cervical rib was anatomically so constituted as to impinge only on the lower cord of the brachial plexus and not on the subclavian vessel.¹³ These considerations shift the emphasis from the pathologic process in the vessel to mechanical irritation of the brachial plexus, and our decision was to perform scalenotomy and resection of the rib without molesting the aneurysm.

The case reported presents a definite history (familial and personal) of hypertensive vascular disease. Hypertension may have been a contributing factor in the development of the local pathologic process. It is interesting that in all four patients the aneurysm was present on the left side, although three of the four presented roentgenographic evidence of cervical rib bilaterally. The dilatation or aneurysm of the subclavian vessel has invariably been found distal (peripheral) to the actual point of impingement of the vessel and the rib, as in our case. There is no adequate explanation of the mechanism involved in their production beyond the law of hydrodynamics which states that reduction in velocity of a fluid flowing through a cylindric channel is attended by an increase in the lateral or wall pressure.¹⁴ Halsted³ undertook the reproduction of the condition experimentally. In two dogs he was

12. Newell, R. L.: Cervical Rib with Vascular Complications, *Brit. M. J.* **1**:782, 1933.

13. Telford, E. D., and Stopford, J. S. B.: The Vascular Complications of Cervical Rib, *Brit. J. Surg.* **18**:557, 1931. Blair, D. M.; Davis, F., and McKissock, W.: The Etiology of the Vascular Symptoms of Cervical Rib, *Brit. J. Surg.* **22**:406, 1935. Newell.¹²

14. Babcock, W. W.: Newer Surgical Methods of Treating Diseases of the Vascular System, *Am. J. Surg.* **16**:401, 1932.

able to produce some degree of dilatation of the abdominal aorta distal to a point of incomplete occlusion by a metallic band and demonstrated a rise in diastolic and fall in systolic pressure beyond the point of constriction.

Within the last month another example of this unusual condition has come to our attention.

A 20 year old waitress was observed during a routine physical examination to present a visibly pulsating expansile tumor in the left supraclavicular fossa. The mass, which was approximately the size of a walnut, was compressible in part. The overlying skin was not adherent and was normal in color and texture. A definite bony prominence could be palpated medial and posterior to the tumor, over which a systolic bruit was present. There was no abnormality in timing or force of the pulses in either upper extremity. Oscillometric readings and skin temperature reactions were within normal limits. There were no trophic disturbances of the fingers or nails. A roentgenogram revealed a well developed cervical rib on the left, which was somewhat larger but otherwise very similar to that of our first patient. There was a soft tissue shadow lateral to the cervical rib in the approximate position of the pulsating tumor. The patient had no symptoms and refused operation after a candid presentation of the problem. In the absence of operative verification, the case can only tentatively be regarded as one of subclavian aneurysm in association with the cervical rib.

ACUTE HEMATOGENOUS OSTEOMYELITIS

CLASSIFICATION OF THE CASES OF ACUTE HEMATOGENOUS OSTEOMYELITIS AS DETERMINED BY THERAPEUTIC INDICATIONS; RESULTS OF OPERATIVE TREATMENT

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In every case acute hematogenous osteomyelitis is basically composed of two components: (*a*) a general bacterial infection (sepsis, septicemia and bacteremia) and (*b*) a local lesion in the bone tissue. In the treatment of this disease in the early stages the most important item is the general infection. The ultimate outcome, death or recovery, depends entirely on this factor, and the mortality statistics of acute hematogenous osteomyelitis in its early stages reflects accurately the mortality of general bacterial infection. When divorced from the general bacterial infection and in the absence of any fatal complications or associated lesions, the mortality of the local osseous lesion is nil.

The treatment of a local lesion of the bone is a problem by itself. In the presence of a general bacterial infection, the latter naturally, must be taken into account. In the absence of any demonstrable evidence of a general bacterial infection, the method of treatment of the local lesion is to be decided on its own merits, as determined by the pathogenesis, by the biologic and anatomicopathologic development and by the physical characteristics of the total resultant lesion.

In this communication a number of cases are described which illustrate the various clinical groupings into which cases of acute hematogenous osteomyelitis can be placed. The groups are differentiated by the relationship of the general infection to the local lesion, by the magnitude of the general infection, by the presence or absence of complications or associated lesions, by the general nature of the pathologic process of the local osseous lesion and by the presence or absence of a well defined abscess. The object of this is to show that the treatment of acute hematogenous osteomyelitis cannot be standardized except as the indications are furnished by laboratory data.

Until recently there existed an almost universal opinion among both medical men and surgeons that urgency in the treatment of acute hematogenous osteomyelitis was a paramount issue if one wished to avoid fatalities because of the general infection, the inference being that as the general infection was derived from the local lesion of the bone, osteo-

tomy, with or without excision of the diseased area, was necessary in order to remove the focus and so control the bacteremia. It will be shown that except in rare instances the inference is incorrect, because operation on the local focus in the bone does not accomplish this object. Either the patient dies irrespective of the operation, or the character of the postoperative course lends itself strongly to the opinion that the operation has had no inhibitory effect on the general infection.

As a corollary to both of these sets of observations it will be shown that urgency in operative treatment is frequently less necessary and less important than intelligent and watchful observation; that rarely, but more commonly than is generally known and understood, foci of hematogenous osteomyelitis subside completely and spontaneously without going on to the stage of necrosis and sequestration; that, similarly, sequestered areas of bone can and do become revascularized and become reincorporated with neighboring normal bone tissue in much the same manner as a bone graft does, and that more frequently than is understood among the general medical profession and among surgeons, operation can be entirely avoided.

Also as a corollary to all of these observations and discussions, it will be shown that operative treatment, when necessary, should not consist of an uncontrolled, vaguely planned and hasty, careless or reckless chopping of bone in areas in which the pathologic process is not always perceptible to the unaided eye, in which the boundaries of normal and diseased bone are not visibly differentiated and in which the possibilities for revascularization cannot be foretold. These are ill designed operations which deal ineffectively with the local lesion. Much harm can and commonly does result immediately, due to the extension of the osseous lesion and/or the production of contiguous complications and, subsequently, the retention of factors which make for recurrences and recrudescences of infection or the production of mechanical conditions which prevent healing.

Finally, it will be shown that operation, when necessary, had best be limited to the simplest of procedures, frequently to the mere incision and drainage of abscesses. In all cases the greatest part of the work must be left to nature, so that avascular areas may be given every opportunity to become revascularized, so that as little as possible of the compromised area shall be irrevocably lost and so that the areas of bone tissue which are lost may be allowed to separate completely from the host and be cast off in the form of a foreign body. Then there will be a minimum of recurrences and recrudescences.

It should be recognized that acute hematogenous osteomyelitis is an incident in a general bacterial infection. Therefore, one may not expect or hope that the mortality of the local lesion (i. e., of the osseous

lesion) will be any less than that of the corresponding and accompanying general infection. It may be taken for granted, except when uncontrollable accidents occur, such as secondary hemorrhage, or when fatal complications are present, such as pericarditis and meningitis, that the mortality of the local lesion is nil. If one keeps these two statements in mind and guides oneself accordingly, much confusion will be avoided.

REPORT OF CASES

GROUP 1.—*Cases in which operation of any kind can be avoided: Subgroup A. Cases with spontaneous early retrogression of the osseous lesion.*

CASE 1 (chart 1).—A young boy was admitted to the hospital with an illness which began one week previously, with pain in the region of the right hip and inability to bear weight on the right leg. The results of the general physical examination were entirely negative. In the region of the right hip there was a tender, hot, red swelling, about the size of the palm, the lesion extending around to the right inguinal region. Clinically, there was no doubt that the pain and tenderness were referable to the bone. There seemed to be evidence, also, of a certain amount of effusion in the right hip joint. The temperature on admission was 104 F. The patient was referred to me for operation for osteomyelitis of the upper end of the femur. However, a conservative policy was followed, and on the day after the patient's admission to the hospital the temperature fell to fairly normal levels, and the local signs improved progressively and markedly and finally disappeared altogether. One week later the patient was discharged from the hospital entirely well.

A blood culture taken on the day of admission was sterile. Roentgen examination made on the fifth day after admission to the hospital showed evidences of a lesion in the neighborhood of the right trochanter, extending upward into the neck, which was undoubtedly an inflammatory process in the substance of the bone.

This case illustrates well the fact that not all forms of osteomyelitis necessarily go on to the stage of suppuration or necrosis of tissue. It must undoubtedly be true that in some cases infection of bone tissue will develop to a certain extent only and will then promptly retrogress to the normal, as is illustrated by this case. In such cases treatment is not needed.

The following case is a typical case of acute hematogenous osteomyelitis. The entire clinical history is available in full, together with complete laboratory data. Only conservative therapeutic measures were employed, and no operation was performed. The patient recovered spontaneously from the acute osteomyelitis and the accompanying general blood infection, with a minimum of structural deformity and with practically no loss or disturbance of normal function. New therapeutic points of view are illustrated by this case which should be stressed. Emphasis is being placed on the criteria on which treatment is based and on the dominating value of laboratory data, especially the blood culture and roentgenographic studies.

Subgroup B. Cases in which the osseous lesions go through a complete development beginning with the stage of bacteremia and continuing through necrosis, sequestration and exfoliation of bone tissue without the necessity for operation and with spontaneous healing and recovery.

CASE 2 (chart 2).—A boy aged 10 years had a congenital cardiac lesion. In January 1927 he had a small furuncle on the chin, which was opened in the outpatient department of the hospital and healed thereafter. The boy was admitted to the hospital one month later with the history that five days prior to his admission he had been kicked in the side, in the general neighborhood of the hip; since then there had developed fever, pain in the general region of the hip and a limp on walking, and all of these signs had progressively increased. On the second day of

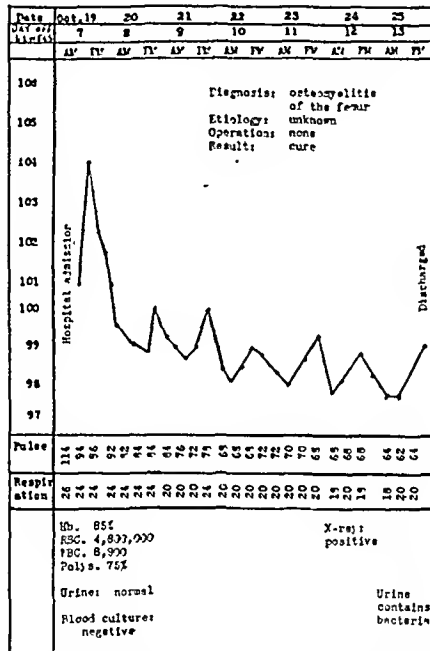


Chart 1.—Clinical record of the patient in case 1. The data presented here are representative of those which are recorded in similar cases, classified as group 1, subgroup A.

the illness the patient had a severe nosebleed. During the course of the illness up to the time of his admission there had been no chills, but he had high fever and became delirious, his temperature on admission to the hospital being 105 F.

Physical examination revealed a very sick, delirious child, in a markedly toxic condition, with a high temperature, signs of a cardiac lesion, a palpable spleen and local objective signs of an infection in the neighborhood of the right hip. It was obvious that a hematogenous infection secondary to the furuncle of the chin was being dealt with. The rôle of the trauma to the side was purely a contingent or contributory one and determined the localization of the secondary focus by creating in some way a locus minoris resistentiae. It was assumed that the infection was seated somewhere in the skeleton in the neighborhood of the right hip, but owing to the diffuseness of the signs of the local lesion and to the lack of any evidence

On the sixty-second day of the illness the patient was discharged from the hospital, free from fever and generally in good condition, with no signs referable to the hip or the pubis and with the foot still swollen but with the condition rapidly subsiding. He was discharged from the hospital with a plaster cast on his foot.

The patient was readmitted to the hospital a number of times thereafter for various complaints. The second admission was for the purpose of renewing the plaster cast. During his third admission a small sinus formed in the perineal region, with practically no inflammatory reaction around it, and from this sinus an inconspicuous fragment of bone was discharged. This occurred three months after the onset of the illness. During the patient's fourth admission to the hospital (1928) an infection developed in the upper part of the right arm, which subsided spontaneously. No osseous lesion could be demonstrated by a roentgenographic examination. During his fifth admission to the hospital (1929) a lesion was demonstrated in the upper end of the left tibia roentgenographically. Treatment was not instituted. Seven years after the onset of this illness and five-years after the last admission to the hospital, the patient died because of the cardiac condition, and during the five intervening years he had no signs referable to the bones of the skeleton or to his preceding infection. As stated previously, the cardiac condition was congenital and had nothing whatever to do with the osteomyelitis or with the general infection.

This case report recounts the history of the development and course of an acute general infection for which the patient was presented for treatment at the stage when an acute osteomyelitis was developing in one of his bones. During the entire clinical course events occurred which were the exact counterpart of events which are being seen repeatedly in similar cases of general infection with secondary foci in the bones and other organs and tissues of the body in which operations are being done and are being repeated for the foci in the bone on the theory that unless operation is done the patient will die of the general infection or that the osseous lesions cannot and will not undergo spontaneous resolution and healing. The fact that operation was not done in this case would seem to indicate that a patient with acute osteomyelitis and general infection, such as this patient had, can recover spontaneously and that operation is not always necessary for the control of the general infection (bacteremia) or for the control and healing of the foci in the bone.

In this patient subsidiary foci developed in other parts of the body (the lung, the upper part of the arm and the tibia). The question arises as to the relationship of these other foci in the pathologic development of the disease. As I have described in my book,¹ each focus in the bone can theoretically act as a secondary point of distribution, so that it is possible (though relatively unlikely) that different crops of lesions may develop, which I have classified as lesions of the second and third order, etc. It might possibly be said that failure to operate on and

1 Wilensky, A. O.: *Osteomyelitis: Its Pathogenesis, Symptomatology and Treatment*, New York, The Macmillan Company, 1934.

eradicate the first of the secondary lesions (in this case the lesion in the ischiopubic ramus) may possibly have allowed the latter to develop to the point where it would act as a secondary point of distribution and through the medium of the consequent secondary bacteremia produce lesions of a second order (in this case, the lung, the upper part of the arm and the tibia).

In this case the pulmonary lesions developed at a point of time relatively close to the onset and development of the primary bacteremia derived from the furuncle on the chin. The lesion on the tibia was discovered approximately two years after the onset of the illness. The biologic characteristics of this lesion as deduced from its morphologic appearances (i. e., that of a Brodie abscess) indicate that at the time of observation it had undergone a period of development which in every one's experience could easily have occupied the space of the intervening two years. The origin of this lesion, too, must therefore be referred to a point in time coincident with the presence of the original bacteremia. The available evidence seems to point strongly to the opinion that under such circumstances all of the foci are to be referred to the primary lesion and are to be considered as secondary lesions of the first order. In addition, when a secondary focus acts as a secondary point of distribution, there are, usually, clinical evidences in the given provocative focus of increased or reawakened pathologic activity. No such clinical fact was observed in this case.

The lesion on the upper part of the arm occurred approximately one year after the origin of the osteomyelitis. There was no clinical evidence of any reawakening of activity in the pubic lesion. As a consequence, there was no reason to connect this infection with the primary infection, and, in addition, it was possible that some wound or abrasion of the fingers or hand might have led to a secondary lymphangitic localization in the arm. In view of these facts, the relative position of this lesion in the total picture is in doubt, and possibly there was no connection between the two.

One should not deduce from this case that every person with acute osteomyelitis of hematogenous origin should be or can be treated in this most conservative manner. There are times and occasions when such a policy would invite disaster. The value of this illustrative case lies in the demonstration of the fact that conservatism can be practiced with safety under well regulated and intelligent observation, and, as experience is gained, more and more frequently; that the clinical course of the illness is not influenced to the extent hitherto believed by early or by any operation, and that there are great advantages to conservatism when it can be practiced, for which radicalism offers no substitute or any advantage, either from the point of view of the period of morbidity and incapacity or relating to anatomic structure and morphology or

to the appearance of the surface and the external contour, or from the point of view relating to the appearance of other foci or even from the point of view of saving life.

GROUP 2.—Cases in which the general infection is the paramount factor and determines the fatal end-result.

CASE 3 (chart 3).—A boy aged 5 years was admitted to the hospital with an area of infection surrounding the right clavicle and with the general signs and symptoms indicating one of the most profound general infections of the hyperacute type which I have ever seen. At the time of his admission the child was in a stupor. In spite of the fact that it was well realized that operation directed to the local focus in the right clavicle would probably be of no avail, the condition seemed most suitable for a total excision of the involved bone, and the latter operation was done forthwith. Nevertheless, this had no effect on the clinical course of the illness, and the patient died.

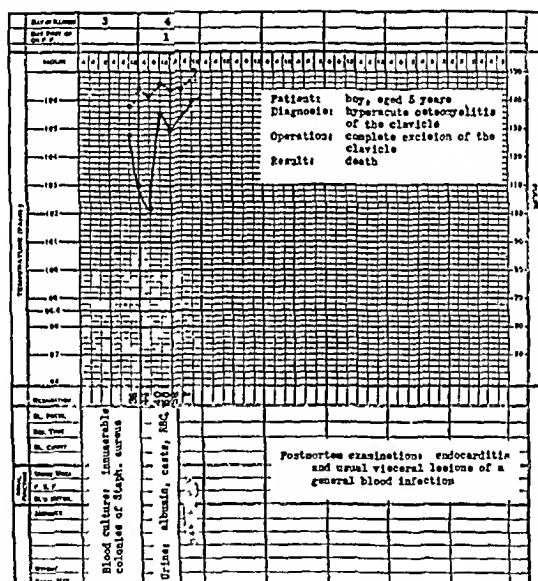


Chart 3.—Clinical record of the patient in case 3. The data presented here are representative of those which are recorded in similar cases, classified as group 1, subgroup B. The solid line indicates the temperature record; the dotted line, the pulse record.

This case illustrates well the futility of operative treatment even of the most radical and maximum type (i. e., amputations and excision of bones in toto) in cases of overwhelming general infection with foci in the bone in which the local lesion is, manifestly, an incident—and a negligible one at that—in the total clinical complex. Occasionally it happens that one is tempted to operate in cases of this type because of extraordinary conditions or associated factors or at the insistence of the patient's family. The effort will, however, be fruitless as death occurs promptly, because of the general infection (bacteremia) and not because of the local lesion.

Compare this case and its chart with the composite chart (chart 4) of the temperature records in four similar cases. Note that the general infection is so overwhelming that the fatality occurs at the peak of the temperature curve in two of the cases. After forty-eight hours the resistance of the patient is completely broken down, so that the temperature reaction is destroyed, and death occurs with the temperature at a low point. This happened in the other two cases.

CASE 4 (chart 5).—Two weeks after an attack of acute tonsillitis and the appearance of several cutaneous furuncles, a youth 20 years of age was admitted to the hospital with a well marked general staphylococcic sepsis and a local lesion in the neighborhood of the knee. On the sixteenth day of the illness some clear greenish straw-colored fluid was obtained from the knee. Cultures of the fluid did not yield any organism. On the eighteenth day of the illness an abscess in the lower and posterior part of the thigh extending into the popliteal space was opened and drained. On the same day a metastatic focus was observed in the sternoelavicular joint.

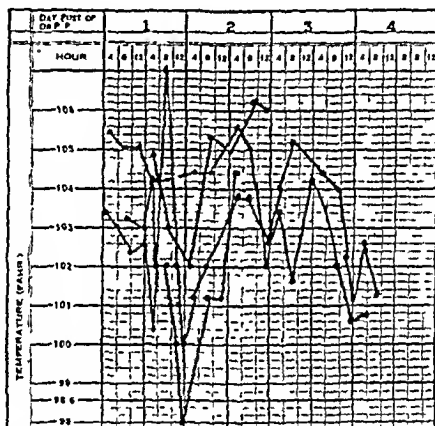


Chart 4.—A composite chart of the temperature records in four cases of acute hematogenous osteomyelitis similar to case 3 (chart 3).

The operation did not cause any appreciable change in the temperature reaction or other general observable clinical facts, and the general infection (sepsis) apparently continued not only unchanged but in increasing intensity, as shown by the blood culture made on the twenty-second day of the illness, when large numbers of colonies were grown in the culture plates. Death occurred on the twenty-sixth day of illness and six days after operation. Postmortem examination showed the osteomyelitic focus in the femur.

This case illustrates the effect of operation on a patient with acute osteomyelitis and a general infection, the severity of which was at first judged to be of moderate grade. It again demonstrates the fact that the local focus in the bone is not the most important factor in the total clinical picture. Contrary to the usual experience, the fixation abscess, which developed in association with the local lesion in the

bone, did not minimize the general infection and its demonstrable bacteremia; instead, the bacteremia became exaggerated, and incision of the abscess made little difference in the observable phenomena of the general infection. The experience also teaches that while incisions of frank abscesses are always indicated, one must not always expect too much from the procedure.

Compare the chart in this case with the composite chart (chart 6) in which are the temperature records from four other cases of acute hematogenous osteomyelitis of severe, though not fulminating, grade of general infection. Operation was performed in three of the cases. The blood cultures were positive in all. Death occurred in all the cases.

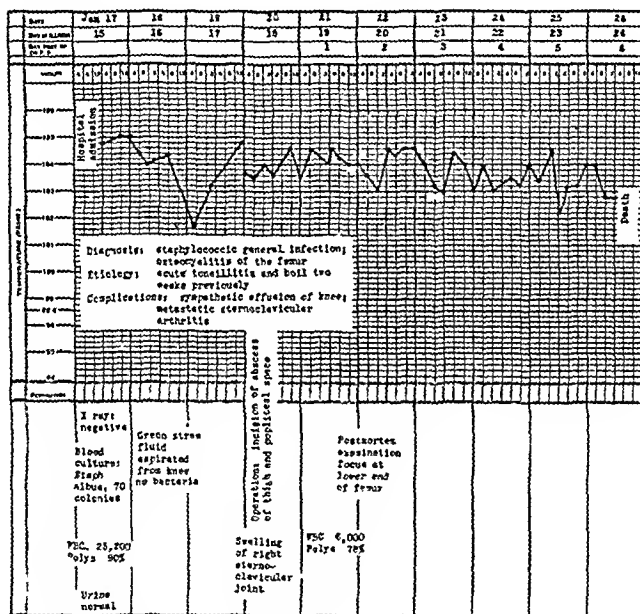


Chart 5.—Clinical record of the patient in case 4. The data here are representative of those which are recorded in similar cases, classified as group 2.

Note that it did not make any difference whether or not operation was performed so far as the postoperative clinical facts and the end-result were concerned, and, again, that the local lesion is a negligible factor. The usual duration of an illness with this grade of infection is about one week.

GROUP 3.—Cases in which the general infection becomes controlled and the end-result depends entirely on the local lesion and/or any intercurrent complication or associated lesions. Subgroup A Cases with fatal end-results because of complications or associated lesions.

CASE 5 (chart 7).—A woman 23 years of age, in previous good health, was admitted to the hospital with the history that three days before her admission the

left lower posterior molar was extracted because it contained a cavity and was impacted and had given rise to a great deal of pain. The dentist who extracted the tooth sutured the wound in the mucous membrane. Afterward an infection developed on either side of the alveolar process in the pretonsillar space and in the submaxillary space on the same side.

The results of the general physical examination were negative. Locally, there were marked swelling, redness and tenderness of the left side of the face and neck. An area of fluctuation was present, and inside the mouth there was a gangrenous infection surrounding the posterior end of the alveolus and in the tonsillar and pharyngeal space. The urine contained albumin but was otherwise normal. The blood culture was sterile. The blood count showed the following: hemoglobin, 64 per cent; red blood cells, 4,370,000; white blood cells, 47,000; polymorphonuclear cells, 95 per cent; band forms, 52 per cent; lymphocytes, 1 per cent; mononuclear cells, 1 per cent, and myelocytes, 3 per cent.

The patient was in the hospital for fifteen days, during which time incisions were made internally in the mouth and externally in the neck for the drainage of collections of pus in the submaxillary triangle and in the interior of the mouth in the pretonsillar space. The posterior parts of the alveolar border of the left side

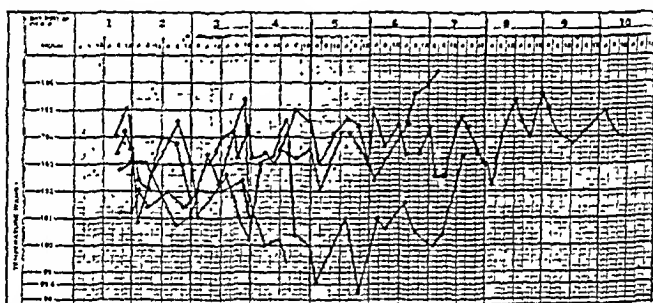


Chart 6.—A composite chart of the temperature records in four cases of acute hematogenous osteomyelitis of severe, though not fulminating grade of general infection.

of the lower jaw were bared and necrotic. The abscesses were characterized by a fetid gangrenous infection, causing necrosis of the entire fascial sheath of the neck, including the deep and superficial cervical fascia and the deep layers extending downward from the latter into the substance of the neck. The infection extended to the right side of the neck and downward into the thorax following the fascial planes, and an abscess developed in the upper anterior portion of the right side of the mediastinum. A focus was also present in the lower lobe of the lung on the same side. It was necessary to revise the operative wounds several times. These findings were abundantly confirmed by roentgenographic studies.

In the last two days of the patient's life there were considerable and increasing oozing and active hemorrhage from the right side of the neck, which was controlled only partially by packing. In spite of the fact that the general condition of the patient was supported by transfusions of blood and in all other possible ways, the patient grew steadily worse and finally died at the end of the indicated period, death undoubtedly being hastened by the continuous hemorrhage.

This case illustrates the fact that patients frequently recover from the original general infection (bacteremia) and then other complications

or associated lesions develop, from the effects of which a fatality occurs. In such circumstances the lesion of the bone, except as it may cause or lead to the complicating fatal lesion (joint infection, hemorrhage and mediastinitis), plays no part in the eventual issue.

GROUP 3.—Cases in which the general infection becomes controlled and the end-result depends on the local lesion and/or any intercurrent complication or associated lesion: Subgroup B. Cases in which both of these factors become controlled and recovery follows.

CASE 6 (chart 8).—In an adolescent boy the extraction of a tooth was followed by a dento-alveolar abscess. About one week later a focus developed in the left radius. At the time of his admission to the hospital the patient was moderately ill,

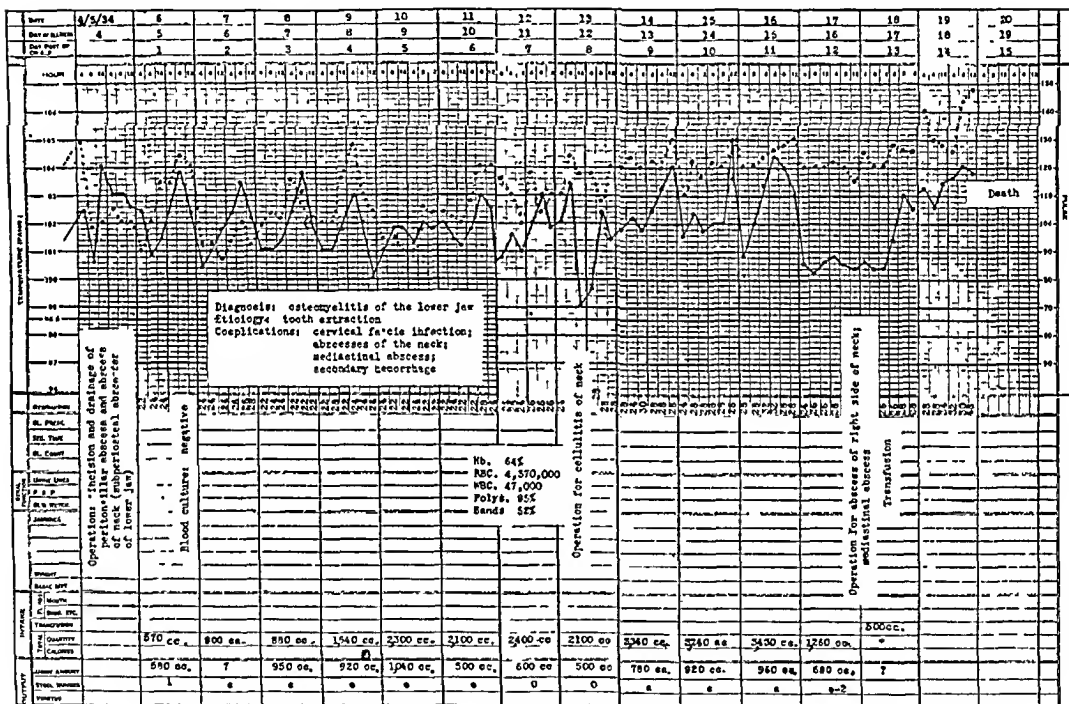


Chart 7.—Clinical record of the patient in case 5. The data presented here are representative of those which are recorded in similar cases, classified as group 3, subgroup A. The solid line indicates the temperature record; the dotted line, the pulse record.

but the blood culture taken before the operation was sterile, and osteotomy was done immediately. The visible signs of the local infection of the bone were definite and well marked. There was a good deal of edema of the periosteum; the bone tissue and the marrow were distinctly inflamed, and there was diffuse supuration but no distinct abscess. Blood culture made directly after operation showed four colonies of *Staph. aureus* for each cubic centimeter of blood cultivated. The pus contained the same organism.

On the fourth postoperative day only one bacterial colony to the cubic centimeter of blood developed in the culture plates. A similar result was obtained on the sixth postoperative day. On the latter day, also, a counterincision was made for the purpose of improving drainage.

On the twelfth day after operation pain and tenderness were noted in the region of the left kidney, and pyuria of moderate extent was present. The urine contained *Staph. aureus*. This was associated with an increase in the temperature. On the fourteenth and fifteenth days after operation the blood cultures were sterile.

An increase in the temperature on the twenty-first day was associated with an arthritis of the left elbow, for which it was necessary to drain the joint.

After the thirty-third day after operation the temperature was normal, and the patient was discharged from the hospital.

This case illustrates the following facts: 1. A complete osteotomy did not improve matters generally.

2. It did not lower the temperature or the pulse rate.

Note especially in this case that so far as the local and general symptoms are concerned, operation had no effect which could be distinguished clinically. This case was one of my earlier ones, seen at a time when I was not so sure of my ground, so that operation was

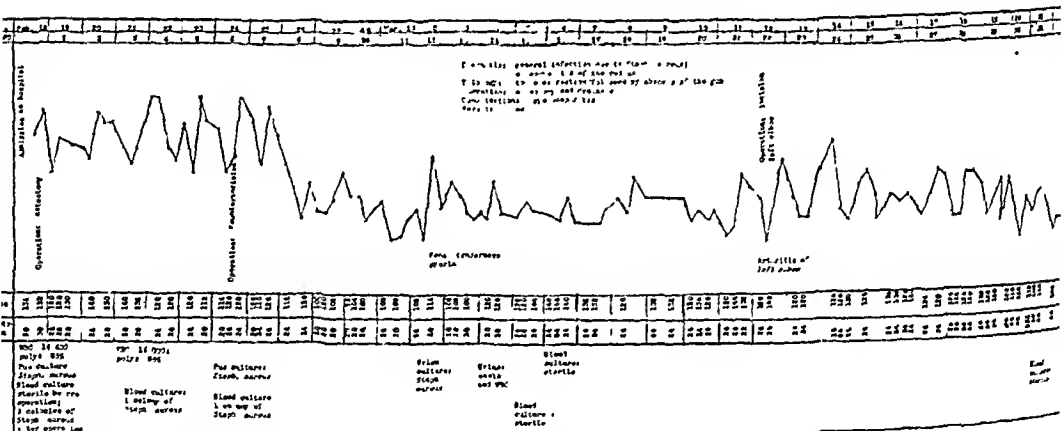


Chart 8.—Clinical record of the patient in case 6. The data presented here are representative of those recorded in similar cases, classified as group 3, sub-group B.

performed. I feel sure that if such a case would present itself today that I should not operate so precipitously; in view of many experiences since, it seems not at all out of the way to think that in this instance the focus would have controlled itself spontaneously and undergone cicatrization and healing without operation of any kind.

Compare chart 8 with chart 9. The latter is a composite chart containing the temperature records obtained in three cases of acute hematogenous osteomyelitis of the ordinary grade and type. The blood cultures were positive in two of the cases and negative in the third. All three patients recovered. Two were operated on during the first week of their stay in the hospital, and the third was not operated on. Note how closely the three temperature curves correspond irrespective of operation. It would not be correct to say that operation had any

effect on the general infection, as evidenced by the temperature curve; the general symptoms and local manifestations corresponded closely to the temperature curve and corroborate this view.

In discussing case 4 (chart 5), it might have been said that the reason no improvement followed the simple incision of the subperiosteal abscess was the failure to perform osteotomy of a more or less radical type and drain the marrow cavity. Case 6 (chart 8) shows that osteotomy did not improve matters in any way and that following operation the condition in each case followed a comparable course. Compare the record of cases 4 and 6 with the composite record in chart 10. The latter is a record of four patients who were treated by various methods. Note how closely the temperature curves correspond. Compare charts 9 and 10. The curves are similar in spite of the fact that they were made in all kinds of cases: those in which operation was performed and those in which it was not and cases in which treatment consisted of simple incision of an abscess and of osteotomy. The comparison shows

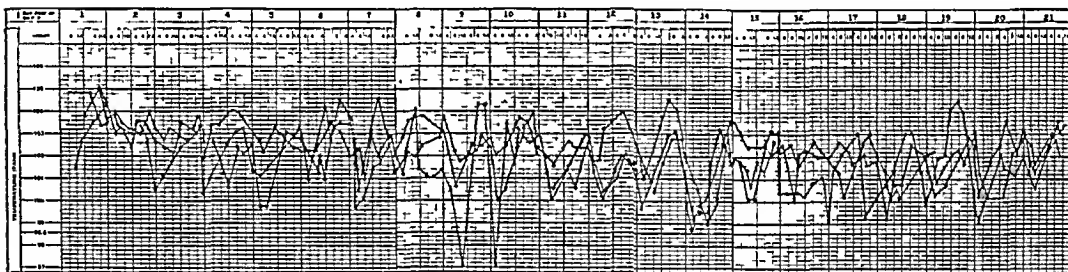


Chart 9.—A composite chart of the temperature records in three cases of acute hematogenous osteomyelitis of the ordinary grade and type.

strongly that the general infection in all these cases is the paramount factor. Recovery occurred in the cases represented in charts 9 and 10.

3. The blood culture became positive after operation.

This is a danger to which one lays the patient open when the seat of the lesion in the bone tissue is cut into with chisel and mallet, because bacterial distribution is mechanically produced from the fixation point in the bone. It is a danger which may not be ignored, and I am sure that it causes more frequently than one cares to admit those recurrences and exacerbations of infection which commonly determine a fatal issue when previously it had seemed that recovery would eventually follow.

4. Operation did not prevent the appearance of other secondary foci.

Recent discussions regarding this point have been limited to two points of view: (*a*) whether the subsequent secondary foci are tributary to the original primary lesion or (*b*) whether they are referable to the focus in the bone acting as a secondary point of distribution. Theoretically

cally, each mechanism is possible. Practically, it is an established fact that most of the secondary lesions occur relatively closely to the time of appearance and development of the original primary lesion, and, as far as one can see, there are no evidences in the osteomyelitic lesion of any extraordinary assumption of activity immediately previous to or at the time other secondary lesions make their appearance. As far as this reasoning goes, it would seem correct to assume that certainly in the greatest number of the cases all of the secondary lesions should be referred to the original primary lesion.

In this case osteotomy was immediately followed by the appearance of a bacteremia of small magnitude. This alters matters considerably, and it is altogether correct to say that secondary lesions which appeared subsequent to the establishment of the bacteremia could most likely be due to it. Such a possibility would point out a distinct disadvantage to osteotomy in the early stages of the osseous lesion. (Compare with item 3.)

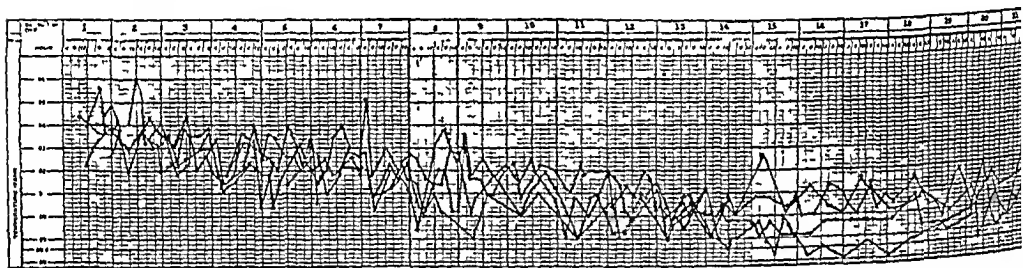


Chart 10.—A composite chart of the temperature records in four cases of acute hematogenous osteomyelitis in which various methods of therapy were used.

5. Locally, operation was followed by infection in the neighboring joint, by subsequent deformity and by eventual loss of function and disability in the joint and limb.

Arthritis in a joint adjacent to a focus of osteomyelitis might be a natural complication and occur spontaneously. On the other hand, assumption of activity in the focus in the bone might cause spreading of the lesion and secondary involvement of the joint, or the joint might be secondarily infected mechanically during the operative manipulations when the anatomic conditions are appropriate. The thoughtful person would immediately recognize the importance of a policy of noninterference when the local and general signs point to the possibility of avoiding osteotomy.

GROUP 4.—Cases illustrating the usual case in which the general infection becomes controlled and the end-result depends entirely on the local lesion in the bone.

CASE 7 (chart 11).—A young child had otitis media and a complicating mastoiditis for which operation was performed. The blood cultures were negative on three occasions. On the sixth day of the illness the blood cultures contained non-hemolytic streptococci, and a thrombosis of the lateral sinus was recognized; the usual operation was done. A remittent fever continued; on the fifteenth day of the illness the blood culture was negative, and a focus in the femur was recognized. Osteotomy was done on the twentieth day of the illness. Subsequently the temperature ran at lower levels and after several weeks came down to normal. The patient was discharged from the hospital on the seventy-first day.

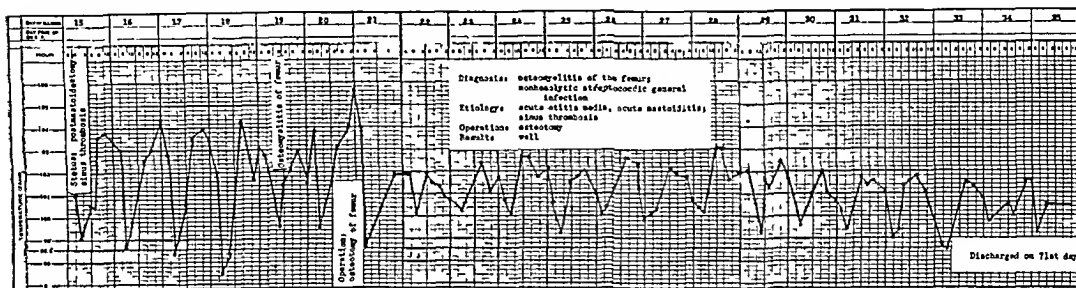


Chart 11.—Clinical record of the patient in case 7. The data presented here are representative of those which are recorded in similar cases, classified as group 4.

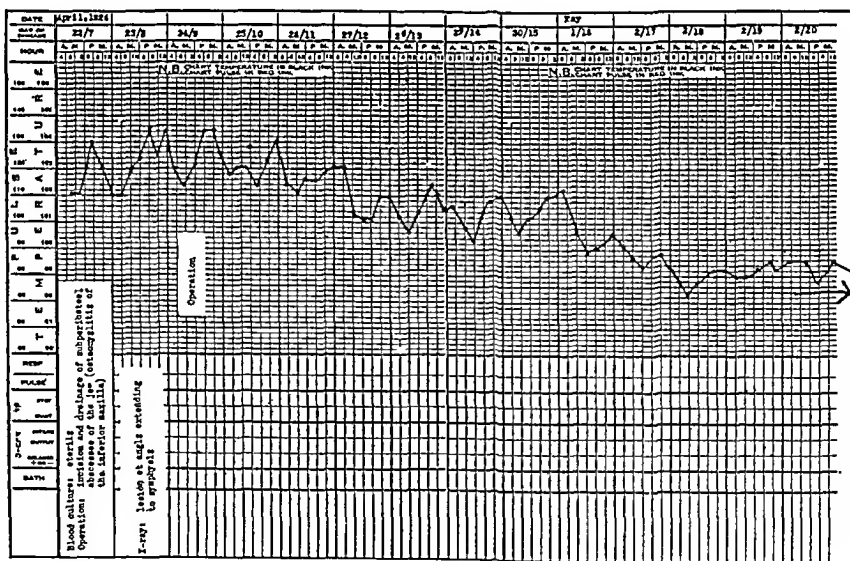


Chart 12.—Clinical record of the patient in case 8, group 4.

CASE 8 (chart 12).—For the usual symptom of pain in one of the teeth of the lower jaw, an extraction had been done about one week previous to the admission of the patient to the hospital. The socket was "lightly" packed. Thereafter progressively increasing pain developed in the lower jaw, the tissues about the jaw began to swell, the swelling becoming more prominent below the ramus of the jaw in the submaxillary triangle. Several incisions were made in the gingivolabial fold by the attending dental surgeon. Pus was not obtained, but the swelling and pain continued to increase.

At the time of the patient's admission, a well defined abscess was present in the submaxillary triangle. A culture of the peripheral blood was sterile.

The submaxillary abscess was incised and drained. Nothing was done to the bone itself nor to any of the teeth. Thereafter the mouth was cleaned regularly with antiseptic washes, and the wound was dressed and cared for in the ordinary surgical way. Under this regimen the amount of discharge lessened and finally became nil; several small and inconsequential sequestrums were discharged from the wound. The wound itself gradually contracted and finally closed and remained closed.

At the peak of development of the pathologic lesion, the roentgenographic studies showed a process involving the horizontal ramus of the lower jaw, extending from near the angle up to the symphysis and across the median line. Although a good deal of destruction was apparently visible in the roentgenogram, nevertheless much revascularization must have occurred because of the inconsequential smallness of the sequestrums, which were discharged.

The cosmetic and functional results are excellent, and there is normal mobility and dental apposition.

The case illustrates the advantages of conservatism when radicalism would lead to unnecessary destruction and loss of bone tissue, to morphologic changes and unnecessary and disturbing anatomic deformity and to disfigurement of the original external contour. Loss of function is prevented (or minimized) because joints are not involved and because the formation of an involucrum is held down to a minimum.

SCIATIC PAIN AND ITS RELIEF BY OPERATIONS ON MUSCLE AND FASCIA

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It has long been known that in many cases continued pain referred to the course of the trunk of the sciatic nerve or to the field of distribution of its two main components, the common peroneal and tibial nerves, the pain may be due to extrinsic pressure by a neoplasm or an infiltration either within the pelvis or outside of it; that the pain at times is caused by a new growth within the spinal canal or by organic disease of the radicles beyond the cord proper; that it is sometimes consequent on disease of the lumbar segment of the spine, and that it may be due to inflammatory disease of the nerve itself, as manifested by those clinical signs on which one must rely, as elsewhere, for the recognition of such neuritis. By these signs is meant impairment of the motor power or disturbance of sensation, either superficial or deep, as well as alteration of the reflexes. From the field of the present discussion it is, however, my purpose to exclude this group of lesions, together with other lesions of an essentially acute and more or less evanescent character. Whatever difficulties they may present, they are involved in no significant obscurity. Quite apart from all of these disturbances is a kind of sciatic pain which may exist for months or years, having irregular remissions or intermissions, but having at the end of such long periods none of the evidences of organic disease of the nerve before mentioned, save perhaps an alteration or absence of the achilles tendon reflex and muscular wasting of an appreciable degree. This type of sciatic pain presents a problem which presses for solution in a manner the more poignant because of the element of chronicity. An orthopedic surgeon is likely to see a patient with sciatic pain only after he has run the gamut of physicians, spas, cultists and downright quacks. Not a few of these patients are in a desperate state of mind and morale. These are the ones who have been told that they have "neuralgia," and their own despair is at times almost equaled by that of the well intentioned medical men who have tried in vain to help them. The term "ischias," or "sciatica," was first used by the Neapolitan anatomist, Cotugno, in 1764. One hundred years later, a notable monograph

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appeared on the same subject by the Parisian clinician and teacher, Lasègue. It is worthy of comment that both Cotugno and Lasègue considered sciatica to be:

. . . a disease and not a functional trouble; it has therefore, a course which is peculiar to it. To represent it simply as a series of attacks of pain is to explain it very badly.

Cotugno considered it due to a dropsy of the nerve sheath. This was, however, pure ratiocination without demonstration. It is interesting, however, that he compared the symptoms to similar ones within the range of the brachial plexus. The similitude was approved by Lasègue, and I shall have occasion to refer to it again.

THE LASÈGUE SIGN

At this juncture, I ask indulgence if I dwell for a moment on the Lasègue sign. As described by Lasègue, it is characterized by pain which is felt either along the back of the thigh or in the region of the sacrosciatic notch when the patient's knee is extended after he has fully flexed the hip joint. While it may be called forth equally well by flexion of the hip after the patient has fully extended the knee, this sign should not be considered synonymous with mere limitation of so-called "straight leg raising." The latter, betokening spasm or contracture of the hamstring muscles, is often present in association with lesions of the lumbar portion of the spine and in such instances without being accompanied by pain in the regions before mentioned. By many writers, including some recent ones, the explanation of the Lasègue sign is easily found in the stretching of the sciatic nerve. However, it is well known that nothing like stretching of the nerve takes place in this maneuver until the hip has been flexed well beyond 90 degrees, a point which is never even approximated in the patient who has a positive Lasègue sign. Moreover, spasm of the hamstring muscles in disease of the lumbar portion of the spine not only is likely to be painless, except possibly in the spine itself, but is apt to occur bilaterally. On the other hand, it is not unusual to find a contralateral Lasègue phenomenon. By this is meant that when the Lasègue maneuver is carried out on the sound side pain is thereby called forth on the affected side. Many patients with sciatic pain are found to have a negative Lasègue sign. Grossman and Keschner¹ in 1929 reported the results of the clinical analysis of a large series of cases of sciatic pain. Their group I was made up of cases in which the pain was obviously to be ascribed to an organic lesion of the nervous system.

1. Grossman, Morris, and Keschner, Moses: *The Sciatic Syndrome*, Arch. Neurol. & Psychiat. **21**:398-412 (Feb.) 1929.

Their group II consisted of 267 cases in which no organic cause for the pain could be established; in 118 of these cases, or 44 per cent, the Lasègue sign was negative. Disregarding my own and much smaller series of recorded cases in which the proportion of positive Lasègue response is much larger, these figures are impressive. Since the group is thus divided into two large categories, an explanation is called for if one is to regard the Lasègue sign of important significance, and the figures themselves would indicate that one should. Grossman and Keschner's group IIb, consisting of 201 cases, represents cases in which there are some indications of an organic change in the nerve. Of these, the Lasègue sign was negative in 43 per cent, whereas in 55 per cent there was a disturbance of the knee jerk. Since the innervation of the quadriceps muscle is entirely outside of the sciatic field, this is important. The segmental innervation of the sciatic field is the fourth and fifth lumbar segments and the first, second and third sacral segments, whereas that of the femoral nerve is the second, third and fourth lumbar segments. Both on anatomic and on clinical grounds, therefore, does it not seem proper to consider these groups of cases separately? In this discussion I shall be concerned only with the situation as it is restricted to the sciatic field. The percentage of cases in which the Lasègue sign is positive and in which the manifestations are found entirely within the sciatic field is sufficiently large to warrant their being placed under a rubric of their own. I have felt for some years that this fact called for an explanation and definition such as had not yet been given. Furthermore, in my own experience, no patient whose reaction to the Lasègue sign was positive and whose symptoms were entirely within the sciatic field has failed to be relieved, even though only temporarily, by means of traction to the extremity made with the hip slightly flexed and in abduction of from 15 to 20 degrees. This appeared to point to a muscular element, even though not certainly.

ANATOMIC RELATIONSHIP OF THE PYRIFORMIS MUSCLE

Anatomic study brought forth the peculiarly close relation between the piriformis muscle and the trunk of the sciatic nerve which is remarked by most anatomists, even though they do not ascribe any practical importance to it. In 1932, in collaboration with Vinke, an anatomic and mechanical study was undertaken with a view of finding a rational explanation. An experimental method on living animals was obviously impossible. Not even the anthropoid apes have an anatomic arrangement of the sciatic field similar to that of man, and information concerning the psychic response to pain would be altogether denied us. The result of our study on fresh cadavers and in

the dissecting room was published in 1934.² We found that Yeoman³ in 1928 had published the first reference to the piriformis muscle in relationship to the cause of sciatic pain. It was felt that an explanation should be forthcoming for the selective effect on the sciatic nerve which is found so frequently, either in connection with the complaints which have been allocated to the sacro-iliac joint or in connection with those referred to the lower lumbar segment. The explanation which has been offered by Goldthwait and Osgood of the proximity of the lumbosacral cord to the sacro-iliac joint should not satisfy one, since mere contiguity and not contact may be spoken of. As Yeoman has pointed out, the piriformis muscle and its fascia are interposed. Moreover, many patients have pain in the lower part of the back and even in the sacro-iliac joints without symptoms of a sciatic nature. It has already been intimated that the assumption of a sciatic neuritis will not answer. Something more is required to explain the considerable number of cases of long duration, extending even throughout years, in which there develop no clinical signs of organic disease of the nerve structure except pain. Little satisfaction is derived from speaking of this as referred or reflected pain, especially in view of the fact that there is a respectable number of cases which appear precisely similar but for the impairment of the achilles tendon reflex and without any other sign of organic damage to the nerve. This is not the picture of chronic peripheral neuritis, nor yet of radiculitis, as one is accustomed to find it under other circumstances. It was felt that another element must be found to explain this localizing effect on the sciatic nerve and more particularly on its component the common peroneal nerve. So commonly are the symptoms found within the distribution of the peroneal nerve that Cotugno himself remarked on the rarity with which the tibial nerve is involved. Therefore, the anatomic study was undertaken, the results of which may be but briefly summarized at this time. We felt justified in making the following conclusions:

1. The piriformis muscle is constantly found to have a part of its origin from the capsule of the sacro-iliac joint, and it is the only muscle which bridges that joint.

2. The piriformis muscle is in extremely close relationship with the sciatic nerve. In 10 per cent or more of cadavers the nerve is found to pass through its substance. Between the piriformis muscle

2. Freiberg, A. H., and Vinke, T. H.: *Sciatica and the Sacro-Iliac Joint*, *J. Bone & Joint Surg.* **16**:126-136 (Jan.) 1934.

3. Yeoman, W.: *Relation of Arthritis of Sacro-Iliac Joint to Sciatica*, *Lancet* **2**:1119, 1928.

and the trunk of the sciatic nerve there is a rich vascular plexus coming from the inferior gluteal vessels; pressure here would call forth a passive hyperemia of the sheath of the trunk of the sciatic nerve.

3. Experiment on cadavers showed that by the Lasègue maneuver the piriformis muscle is put on the stretch after only a few degrees of straight leg raising through the medium of the biceps femoris muscle and its connection with the great sciatic ligament from which the piriformis muscle derives a part of its origin uniformly. Since part of the piriformis muscle is constantly derived also from the capsular ligament of the sacro-iliac joint, it may be expected to react by spasm as the result of disease in this joint. It may conceivably be involved by direct extension of disease from the sacro-iliac joint, or independently.

It is important to bear in mind the anatomic relationships shown in the illustrations in connection with the effects of certain surgical procedures which will be referred to presently. The following anatomic facts seem to be entitled to special emphasis. Since either the trunk of the whole sciatic nerve or, more often, the peroneal component of it perforates the piriformis muscle in a considerable proportion of persons, the possibility of direct involvement of nerve must be granted in case of disease or spasm of the muscle. Even when this is not the case, the nerve lies directly against the bone of the great sciatic notch and may, conceivably, be compressed on it by the piriformis muscle, inflamed or spastic, as the case may be. The gluteus maximus muscle, one of the most powerful and bulky muscles of the body, overlies the piriformis muscle directly. That considerable part of it which does so inserts chiefly into the fascia lata, on the state of tension of which its own tonicity is conditioned. It follows that with marked impairment of this tonicity there will result a definite diminution of tension over the piriformis muscle on the one hand and a similar hypotensive effect on the lower portion of the lumbodorsal fascia on the other hand. While the function of the gluteus maximus muscle as a part of the tensor mechanism of the thigh has been recognized by anatomists, it is likely that the magnitude of the rôle that it thus plays has hitherto not been realized. It may be observed here that in the severe flexion contractures of the hip which one often sees as the result of poliomyelitis sciatic pain is not present, although abductor contracture of the iliotibial band is most often associated with it. Here, however, paralysis of the gluteus maximus muscle is commonly dealt with, and it is therefore flaccid. Even should one grant such a possibility, therefore, one cannot expect a compressive effect on the piriformis muscle under these circumstances.

PRACTICAL DEDUCTIONS

The effect of our anatomic study was to make us believe that the relationship of the piriformis muscle to the sciatic nerve is of practical importance. In concluding the original paper, surgical attack on the piriformis muscle was merely alluded to. By the time of its appearance in print this had already been carried out in several cases which were considered appropriate. It is not the present purpose to dis-



Fig. 1—Drawing showing the portion of the fascial origin of the piriformis muscle (*A*) which springs from the capsule of the sacro-iliac joint (*B*). This slip of origin is seen to the right of *B*. *C* indicates the obturator internus muscle (Modified from Toldt: *J. Bone & Joint Surg.* **16**:126-136 [Jan.] 1934. This illustration is reproduced by permission of the publishers.)

cuss the general diagnosis of sciatic pain. On the contrary, it is proposed to assume the exclusion of all cases of pain due to disease of the central nervous system, those of pain due to neoplastic or inflammatory disease of viscera and those in which the basis is a frankly recognizable disease of the spinal radicles or of the sciatic nerve and

its components. It has been known for some years, particularly to the orthopedic surgeon, that many patients with sciatic pain which was felt to be attributable to a lesion of the sacro-iliac joint have responded remarkably well to traction applied to the lower extremity in the position of moderate abduction and flexion of the hip. When this happens, relief is likely to be experienced within forty-eight hours. In a certain number of cases, and especially in those in which the

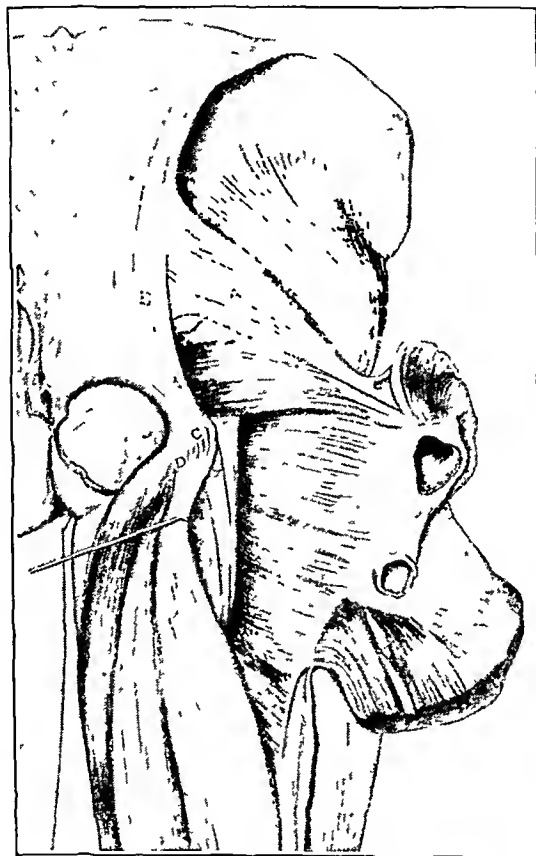


Fig. 2.—Drawing showing the sacrotuberous ligament (B) and above it the fascial origin of the piriformis muscle (A) springing from it. At C is shown the continuity of fibers from the tendon of the biceps with those of the sacrotuberous ligament. When the biceps is put on the stretch, as in the straight leg-raising or the Lasègue test, the piriformis muscle is also made taut. (Modified by Toldt: *J. Bone & Joint Surg.* **16**:126-136 [Jan.] 1934. This illustration is reproduced by permission of the publishers.)

pain is not of very long duration, the relief is continuous, particularly if mechanical support of the lower part of the back is provided. In a few instances, however, especially in those in which the condition

is of long duration, pain recurs when traction is discontinued and activity is resumed. In such instances further help is demanded. Nerve stretching has been done in the past with little satisfaction, according to most reporters, and various methods of injection have been employed without conspicuous success. Were this otherwise, this whole discussion would be superfluous. So, too, has passed the vogue for forcible manipulation, the issue of which was at times very unhappy. There followed a period of operative intervention, ushered in by Smith-Petersen with fusion of the sacro-iliac joint. Other operations were also employed, such as fusion of the lumbosacral articulation and attack on the articular process of the fifth lumbar vertebra, according to

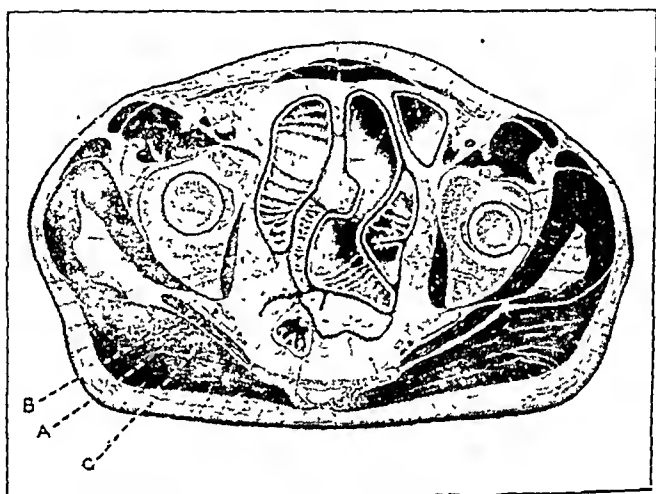


Fig. 3.—A cross-section just above the trochanter major. Here the trunk of the sciatic nerve lies directly on the iliac bone at the notch (*A*); the piriformis muscle (*B*) is in close contact with it posteriorly and separated from it only by its thin, enveloping layer of fascia. In immediate contact with the piriformis muscle posteriorly is the large mass of the gluteus maximus muscle (*C*), which inserts in considerable part into the fascia lata. According to Braus, the greatest part of the fibers of the gluteus maximus muscle arise from the sacrotuberous ligament; some of them arise from the lumbodorsal fascia. Through these, the action of the muscle is transmitted to the spinous processes of the lowermost lumbar vertebrae. (From Eycleshymer and Shoemaker: *Cross Section Anatomy*, section 40. Published by permission of D. Appleton-Century Company, Inc., New York.)

whether the sponsors attributed the symptom to lesions or to structural abnormalities in that situation. For the most part the operations involved have been of no mean gravity to the patient and have required long periods of convalescence, nor have they been without difficulty to the operator. There is no question but that fusion of the sacro-iliac joint was done in many cases with definite success; in not a few the

operation failed of such reward. The cause for failure, of course, may have lain in faulty diagnosis.

The first case in which an operative attack was made on the piriformis muscle for sciatic pain was that of a woman 30 years of age. Partial thyroidectomy had been done about ten months before, because of hyperthyroidism of atypical character. Traction had furnished only temporary help. Fusion of both sacroiliac joints had been done by the Campbell, or extra-articular, method. Relief following these operations did not endure. Seven months after the second of the fusion operations had been done, the patient returned, pleading for relief. Careful study failed to show any cause in the nervous system or, indeed, elsewhere. The Lasègue sign was positive, and there was tenderness over the sciatic notch of both sides. Section of the piriformis muscle was done on one side, and the patient was sent home in a few days, free from pain on this side and with instruction

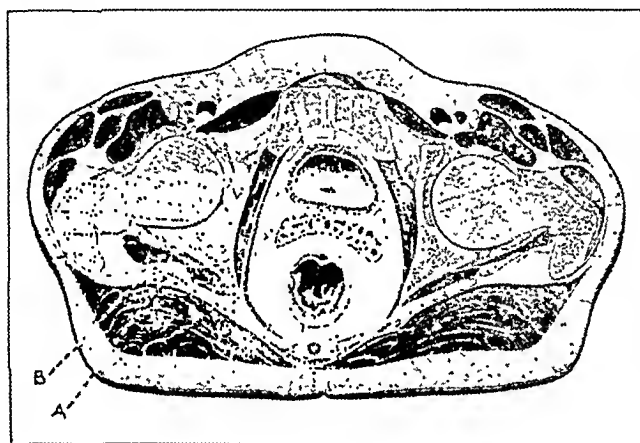


Fig. 4.—A cross-section made just below the tip of the trochanter major. Here the obturator internus and the gemelli muscles (*B*) are interposed between sciatic nerve (*A*) and bone. (From Eycleshymer and Shoemaker: Cross Section Anatomy, section 41. Published by permission of D. Appleton-Century Company, Inc., New York.)

to return should she desire the operation done on the other side. She returned in less than one month, asking for the second operation; this also was successful. A letter was received from her two years afterward expressing her gratitude for the continuance of complete comfort; she had recently been married and inquired about the risk of maternity.

OTHER EXPLANATIONS

Since the appearance in January 1934 of the two communications on this subject with which I have been associated, two contributions of significance have been made which concern themselves with operative procedures. In October 1934 Heyman⁴ described two cases in which

4. Heyman, C. H.: Thoughts on Relief of Sciatic Pain. *J. Bone & Joint Surg.* 16:889-894, 1934.

immediate relief was given and maintained by subperiosteal stripping of the gluteus maximus muscle and ligaments from the posterosuperior spine of the ilium. In his second case both forcible manipulation and fusion of the sacro-iliac joint had been done without abiding relief. The Lasègue sign was positive in both cases. He expressed the belief that his experience eliminates the pyriformis muscle from the discussion in these two instances.

In May 1935 Ober⁵ published a paper on back strain and sciatica in which the ground is taken that the iliotibial band is an exceedingly important factor in the occurrence of lame back, with or without associated sciatica. He described the condition of abduction contracture of the hip joint which he found in such cases, as well as the method of recognizing it clinically. An account is given of a number of cases in which prompt and satisfactory relief was given by incision of the iliotibial band below the anterior superior iliac portion of the spine. There is no disposition whatever to question the claim of relief by this means; indeed, it has been possible for me to substantiate this by several such operations, done consequent on this publication. However, the aid which is brought to a patient with sciatic pain by this means brings with it questions the answers of which it would seem important to find. Ober's explanation is:

First, that the shortness of the iliotibial band and the contracture of the fascia lata cause a squeezing effect on the sciatic nerve where it passes over the acetabulum. Second, an explanation which seems more reasonable, that the mechanical pull on the contracted bands or band is producing a mechanical strain of the sacro-iliac or lumbosacral articulation.

However, both these explanations seem to me inadequate: the first, because the relationship to the acetabulum is not close enough; the second, because it has hitherto not been clear why a lesion of the sacro-iliac joint should produce sciatic pain. In the case of a structurally normal sacrolumbar joint it is still less so. Examination of persons without either sciatic pain or pain in the back has shown in several instances the existence of well marked abduction contracture of the hip. On the other hand, in a number of cases of long-continued sciatic pain which were otherwise precisely similar, so far as we could tell, there was ascertainable no abductor contracture of the hip whatever. One is, furthermore, entitled to ask: Why are some abductor contractures of the hip productive of lame back without sciatica and why some others of sciatica without lame back? The obvious answer would be that there are other accompanying conditions, either in the sacro-iliac or in the lumbosacral joint, which determine such localization of

5. Ober, F. R.: Back Strain and Sciatica, J. A. M. A. **104**:1580-1583 (Mar 4) 1935.

symptoms. It seems much more rational to say that when incision of a contracted iliotibial band brings relief from sciatic pain it is because relaxation of the general tension of the fascial tube of the thigh and more especially of the fibers of the gluteus maximus muscle brings release of pressure on a piriformis muscle and sciatic nerve which are under abnormal conditions to begin with.

A man approaching 50 years of age, who was operated on only recently, presented severe sciatic pain, which had recurred after being relieved by long-continued fixation in a plaster cast and rest in bed. Evident structural damage to the sacro-iliac joint was observed in the roentgenogram; the lesion, while not extensive, appeared to be destructive, and there was a positive cutaneous reaction to tuberculin in a dilution of 1:10,000. The achilles tendon reflex was markedly impaired, but no sensory or other reflex disturbance could be found. The Lasègue sign was positive, and there was marked and constant tenderness at the sciatic notch and over the mesial part of the piriformis muscle. The Ober sign of abduction contracture of the hip was definitely positive on both sides. Accordingly, incision of the iliotibial band was done on the side of the sciatic pain, local anesthesia being used. Prompt subsidence of the pain resulted, and the condition has remained entirely satisfactory thus far.

In contrast to this case, I wish to cite another, that of a traveling salesman approaching 40 years of age. He was well except that for two years he had been suffering from pain in the lower part of the back, radiating down the back of the left thigh and latterly extending to the foot. The pain had been excruciating and interfered greatly with sleep. He had worn various supports and had tried different kinds of treatment without result. General examination gave essentially negative results. The Lasègue sign was positive on the left, and there was marked tenderness of the lower part of the left sacro-iliac joint, particularly at the sciatic notch. The achilles tendon reflex was exceedingly weak. Vibration sense was normal, and so were the results of all tests for cutaneous sensibility. The Ober test for abduction contracture was, however, indubitably negative on both sides. On July 22, 1935, the piriformis muscle was exposed and incised between clamps. About $\frac{1}{2}$ inch (1.3 cm.) of it was excised, and the ends were ligated with catgut. The trunk of the sciatic nerve was exposed; it appeared to pass anterior to the whole of the belly of the piriformis muscle, so far as could be seen, but the critical portion of the muscle could not well be disclosed in this wound. The man was at once relieved and has remained so, being last seen on Dec. 21, 1935.

In both of the cases just reported the patient was subjected to thorough general, serologic, visceral and neurologic study before we arrived at any conclusions. I have omitted details to avoid prolixity.

These two cases would appear to illustrate two interesting things: in the first instance, that sciatic pain which I, at least, felt should be attributed to the piriformis muscle could be relieved by cutting the iliotibial band when in contracture; in the second, that sciatic pain similarly charged to the piriformis muscle and entirely relieved by its section could exist in the absence of the Ober sign of abduction contracture. It would therefore appear possible to have abductor contracture without either pain in the back or sciatic pain, just as it appears

possible to have sciatic pain of the kind being considered in the absence of the Ober sign. On both anatomic and clinical grounds, the conclusion which I draw is that the operations of Heyman and Ober alike owe what effectiveness they have to their action through the gluteus maximus muscle, so far as sciatic pain is concerned, but that it is through the medium of the piriformis muscle after all. Because of its more superficial location, the procedure of Ober on the iliotibial band is somewhat simpler than myotomy of the piriformis muscle. Nevertheless, the operation on the piriformis muscle, also, is easily done with local anesthesia. With us, the iliotibial band has been cut for sciatic pain with the feeling that the operation on the piriformis muscle was still available in case of need. But it does seem illogical to divide the iliotibial band when there is no evidence of its contracture, and sufficient warrant appears for believing that this happens in cases of sciatic pain which in all other respects belong in the same grouping. In a personal communication, Dr. Leo Mayer, of New York, has described a case in which sciatic pain was relieved by incision of the iliotibial band but recurred after six weeks. The question thus arises whether in the presence of such contracture not only the iliotibial band but also the piriformis muscle should be incised.

I shall not fail to emphasize my realization of the fact that in both of these operations one is most often dealing with what is merely a symptomatic release. Unless one credits the muscle or the fascia, as the case may be, with being the seat of the primary lesion this will be true. While this may be the case, it is in my opinion most often not so; in the contrary event, it will be difficult to determine this definitely. Thus far, the proposal to relieve sciatic pain by operation on the piriformis muscle has been made only for patients who have their symptoms entirely within the field of sciatic distribution. Perhaps in the future it may be found undesirable to restrict its use thus. I must not omit to state, however, that whereas cases are observed in which the clinical study points to the piriformis muscle as the direct cause of pain, at the same time there is reason to believe that this is incidental to disease in the sacro-iliac joint and that the sacrolumbar and even the lumbar segment of the spine may also be implicated. It would obviously constitute an inexcusable error to look on an operation on the muscle or fascia to relieve pain as fulfilling one's task when one's responsibility demands that this be followed by the mechanical and constitutional measures which are calculated to control the fundamental condition which has occasioned the pain. I fear that I have already observed evidence of such a mistaken attitude toward these operations. Unless such precaution is heeded one may expect recrudescences, which are avoidable.

In Lasègue's⁶ monograph there is a statement which has intrigued me. He said:

My conviction is that the study of the diseases of the brachial plexus should parallel those of the sciatic plexus; that their differences provide as much information as their resemblances. It is regrettable that Cotugno, having had the primary idea, should have abandoned it hastily, instead of pursuing it.

This statement came back to me recently when my attention was attracted to an article by Ochsner, Gage and DeBakey.⁷ There is here described what the authors term "a clinical entity, the symptoms of which are identical with those of cervical rib. . . . The treatment consists of resection of a portion of the scalenus anticus muscle." It does not seem opportune to enter further into the discussion of this phase now. Suffice it to say that while the anatomic conditions are by no means the same, neither may they be said to be entirely heterologous nor the analogy altogether fantastic.

CONCLUSIONS

Even though I deem it scarcely necessary at this juncture to insist again on the primary necessity of making the general examination with exacting care and thoroughness in order that a correct diagnostic conclusion may be reached before advocating such operative measures as have been set forth, I shall not forbear from so doing. This having been complied with, I still plead for a wise conservatism. I am much too cognizant that in the past many patients belonging in the class under discussion have been brought to cure without operation whether by means of traction and mechanical support or by means of epidural or paravertebral injections. This is not to say, on the other hand, that it is justifiable to prolong unduly the period of distress or invalidism in order to avoid an operation which in skilled hands is free from danger as well as from later undesirable consequences. No patient who has thus far been operated on has shown any loss of function. There remain to be stated the conditions under which it has thus far been felt justifiable to do section of the pyriformis muscle, that of the iliotibial band or the two combined, even though I have not yet advocated the combined procedure in any case. Once the diagnosis appears sufficiently clear, the primary considerations involve the questions of chronicity, of severity of pain and of recurrence after relief has been secured by other means. The determining criteria which give promise for the favorable outcome of the operation are: a positive Lasègue sign, tender-

6. Lasègue, C.: *Consideration sur la sciatique*, Arch. gén. de méd. 2:558, 1864.

7. Ochsner, Alton; Gage, Mims, and DeBakey, Michael: *Scalenus Anticus Syndrome* (Naffziger), Am. J. Surg. 28:669-696, 1935.

ness at the sciatic notch and definite relief from traction properly applied. I feel that it is too early to say that there are precise data on which to base a preference for section of the piriformis muscle; my reasons will be apparent from what I have already said. Neither am I ready to say that fusion operations are to be entirely abandoned. I do say, however, that by means of these myofascial operations the field of fusion has been greatly narrowed, perhaps to the degree of reserving it for certain cases of destructive disease.

In conclusion, it seems entirely justifiable to say that by means of these relatively simple and safe procedures one is enabled to offer a new hope to a group of patients to whom, until now, professional efforts had seemed well nigh fruitless and illusory. I am convinced that there are more of them than many have believed. It is no small thing for them or for the surgeon to be able to supplant their despair by surcease of suffering.

PARA-AMINOBENZENESULFONAMIDE AND ITS DERIVATIVES

CLINICAL OBSERVATIONS ON THEIR USE IN THE TREATMENT OF
INFECTIONS DUE TO BETA HEMOLYTIC STREPTOCOCCI

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During the past three years an ever increasing volume of favorable reports¹ have emanated from Europe concerning the use of para-aminobenzenesulfonamide and its derivatives in the treatment of infections due to beta hemolytic streptococci. During the past few months we have had the opportunity of employing these new specific chemotherapeutic agents in the treatment of experimental and clinical infec-

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1. (a) Foerster: *Zentralbl. f. Haut- u. Geschlechtskr.* **45**:549, 1933. (b) Grütz, O.: *ibid.* **49**:300, 1934; *Med. Klin.* **30**:52, 1934. (c) Veil, W.: *Therap. d. Gegenw.* **75**:212, 1934. (d) Gmelin, L.: *München. med. Wchnschr.* **82**:221, 1935. (e) Domagk, G.: *Deutsche med. Wchnschr.* **61**:250, 1935; *Angew. chem.* **48**:657, 1935. (f) Klee, P., and Romer, H.: *Deutsche med. Wchnschr.* **61**:253, 1935. (g) Schreus, H.: *ibid.* **61**:255, 1935. (h) Anselm, E.: *ibid.* **61**:264, 1935. (i) Gantenberg, R.: *ibid.* **61**:284, 1935. (j) Gantenberg, R., and Thimme, B.: *Med. Welt* **9**:1009, 1935. (k) Imhaeuser, K.: *Med. Klin.* **31**:282, 1935. (l) Schranz, H.: *München. med. Wchnschr.* **82**:419, 1935. (m) Levaditi, C., and Vaisman, A.: *Compt. rend. Acad. d. sc.* **200**:1694, 1935; *Compt. rend. Soc. de biol.* **119**:946, 1935. (n) Nitti, F., and Bovet, D.: *ibid.* **119**:1277, 1935. (o) Recknagel, K.: *München. med. Wchnschr.* **82**:704, 1935. (p) Bingold, K.: *ibid.* **82**:871, 1935. (q) Einhaeuser: *ibid.* **82**:1463, 1935; *Deutsche med. Wchnschr.* **61**:1263, 1935. (r) Fuge, K.: *ibid.* **61**:1263, 1935. (s) Roth, A.: *ibid.* **61**:1734, 1935. (t) Puschel, E.: *Fortschr. d. Therap.* **11**:96, 1935. (u) Temming, H.: *Kinderärztl. Praxis* **9**:400, 1935. (v) Fasal: *Med. Klin.* **31**:898, 1935. (w) Tréfouel, J.; Nitti, F., and Bovet, D.: *Compt. rend. Soc. de biol.* **120**:756, 1935. (x) Riecke, H.: *Ztschr. f. Hals-, Nasen- u. Ohrenh.* **38**:175, 1935. (y) Tixier, L., and Eck, M.: *Bull. Soc. de pédiat. de Paris* **33**:493, 1935. (z) Lampert, J.: *Zentralbl. f. Chir.* **62**:2947, 1935. (a') Scherber, G.: *Wien. med. Wchnschr.* **85**:284, 346 and 783, 1935; **86**:22, 1936. (b') Bloch-Michel, H.; Conte, M., and

(Footnote continued on next page)

tions produced by beta hemolytic streptococci. We have discussed our preliminary observations in a previous report.² In this communication we shall describe briefly the action of the compounds which we have tested and detail our experiences in the clinical use of para-aminobenzenesulfonamide and its derivatives in the treatment of human beings with infections due to hemolytic streptococci.

EXPERIMENTAL OBSERVATIONS

In the course of our investigations we have used two samples of para-aminobenzenesulfonamide, one supplied to us by E. I. DuPont de Nemours and Company and the other by the Winthrop Chemical Company. Two derivatives of this substance have also been studied. One of these, the hydrochloride of 4'-sulfamido-2, 4-diamino-azo-benzene was sent to us in tablet form, labeled "prontosil tablets," while the second, the disodium salt of 4'-sulfamidophenyl-2-azo-7-acetyl-amino-1-hydroxynaphthalene-3, 6-disulfonic acid, was supplied to us as a red liquid, labeled "prontosil, 2.5 per cent solution." Tablets containing 0.3 Gm. of para-aminobenzenesulfonamide in a starch base, labeled "prontylin," were also used in our experimental and clinical investigations. All three of the preparations bearing trade-marked names were supplied by the Winthrop Chemical Company.

Our preliminary observations confirmed the report of Colebrook and Kenny^{1*} that prontosil solution had little if any effect on hemolytic streptococci in vitro. However, we soon observed that a concentration of 1:10,000 of para-aminobenzenesulfonamide had a marked bacterio-

Durel, P.: *Presse méd.* **44**:1583, 1935. (c') Buttle, G.; Gray, W., and Stephenson D.: *Lancet* **1**:1286, 1936. (d') Caussé, Loiseau, and Gisselbrecht: *Ann. d'oto-laryng.*, February 1936, p. 194. (e') Colebrook, L.; Buttle, G., and O'Meara, R.: *Lancet* **2**:1323, 1936. (f') Colebrook, L., and Kenny, M.: *ibid.* **1**:1279, 1936; (g') **2**:1319, 1936. (h') Doerfler, H.: *München. med. Wchnschr.* **83**:1913, 1936. (i') Domagk, G.: *Klin. Wchnschr.* **15**:1585, 1936. (j') Férey, D.: *Bull. méd., Paris* **50**:230, 1936. (k') Floch, H.: *Bull. Soc. path. exot.* **29**:165, 1936. (l') Gley, P., and Girard, A.: *Presse méd.* **44**:1775, 1936. (m') Goissedet, P.; Despois, R.; Gailliot, P., and Mayer, R.: *Compt. rend. Soc. de biol.* **121**:1082, 1936. (n') Hörlein, H.: *Proc. Roy. Soc. Med.* **29**:313, 1936. (o') Kramer, W.: *München. med. Wchnschr.* **83**:608, 1936. (p') Lemierre, A.; LaPorte, A.; Laudat, M., and Daum: *Bull. et mém. Soc. méd. d. hôp. de Paris* **52**:535, 1936. (q') Levaditi, C., and Vaisman, A.: *Compt. rend. Soc. de biol.* **121**:803, 1936. (r') Ley, L.: *München. med. Wchnschr.* **83**:1092, 1936. (s') Meyer-Heine, A., and Huguenin, P.: *Presse méd.* **44**:454, 1936. (t') Sigel, O.: *Fortschr. d. Therap.* **12**:229, 1936. (u') Vermelin and Hartmann: *Bull. Soc. d'obst. et de gynec.* **25**:158, 1936.

2. Long, P. H., and Bliss, E. A.: *Para-Amino-Benzene-Sulfonamide and Its Derivatives: Experimental and Clinical Observations on Their Use in the Treatment of Beta-Hemolytic Streptococcic Infection: a Preliminary Report*, J. A. M. A. **108**:32 (Jan. 2) 1937.

static action on beta hemolytic streptococci when tested in vitro in the presence of beef infusion broth or 50 per cent normal horse serum broth. This observation has been independently arrived at by Colebrook and his co-workers.^{1e}

It had been shown by Domagk and Colebrook and Kenny and others³ that while prontosil solution was inactive in vitro, it had a very active chemotherapeutic effect in vivo. In our previous report we postulated the hypothesis that a reduction of the chemical substance in prontosil solution occurred in vivo in the presence of infection and that the reduced form represented para-aminobenzenesulfonamide. We have been able to repeat this observation in vitro by demonstrating the bacteriostatic action of prontosil solution that has been reduced to the active form by cysteine hydrochloride.⁴

The importance of the rôle of reduction in the activation of prontosil solution has been recently and independently pointed out by Colebrook and his co-workers.^{1e}

In our previous communication² we reported that we had been able to confirm in part the reports of European investigators⁵ regarding the efficacy of these chemotherapeutic agents in the treatment of infections produced experimentally in mice with beta hemolytic streptococci. Our immediate results compared favorably with their results. However, we have now to report that mice have died of streptococcic infection as late as seventy-four days after the infection or sixty days after treatment with prontosil solution had been discontinued. During the interval the mice had apparently enjoyed good health, but still they succumbed to the original infection after this relatively long period. These late deaths cannot be explained at the present time. It should be noted, however, that the strains we employed in our experimental observations had a high virulence for mice, a hundred millionth of a cubic centimeter of the twelve hour blood broth culture containing from two to five minimal lethal doses, so that if one streptococcus survived it would presumably be capable of multiplying and eventually killing a mouse.

Experimental observations on the mode of action of these compounds lead us to believe that they act by inhibiting the growth of beta hemolytic streptococci and that they injure these organisms in such a way as to permit them to be phagocytosed by the white blood cells. Recent observations on the exudate in experimental streptococcic peritonitis in mice have shown that inhibition of growth and phagocy-

3. Domagk.^{1e} Colebrook, Buttle and O'Meara.^{1e} Colebrook and Kenny.^{1f} Colebrook and Kenny.^{1f}

4. Bliss, E., and Long, P.: Bull. Johns Hopkins Hosp., to be published.

5. Domagk.^{1e} Levaditi and Vaisman.^{1m} Nitti and Bovet.¹ⁿ Tréfouël, Nitti and Bovet.^{1w} Colebrook and Kenny.^{1f}

tosis of the organisms occur about six to eight hours after the injection of the chemotherapeutic agent into the animal body. This lag in action suggests the possibility of a change in the chemical substances after their introduction into the animal organism.

CLINICAL OBSERVATIONS

We have used the following preparations in the treatment of human beings with infections due to beta hemolytic streptococci:

1. A 2.5 per cent solution of the disodium salt of 4'-sulfamido-phenyl-2-azo-7-acetyl-amino-1-hydroxynaphthalene-3, 6-disulfonic acid, labeled "prontosil, 2.5 per cent solution." This preparation was always used parenterally.

2. Tablets containing 0.3 Gm. of the hydrochloride of 4'-sulfamido-2, 4-diamino-benzene, labeled "prontosil tablets." (This compound is no longer available.)

3. Tablets containing 0.3 Gm. of para-aminobenzenesulfonamide, labeled "prontylin."

4. Two samples of chemically pure para-aminobenzenesulfonamide.

With these preparations, singly and in combination, we have treated seventy persons ill with infections due to beta hemolytic streptococci. The types of disease treated and the results of treatment are given in the accompanying table.

Types of Infections Produced by Beta Hemolytic Streptococci Treated with Para-Aminobenzenesulfonamide and Its Derivatives

Type of Infection	No. of Patients	Recovered	Died
Erysipelas and cellulitis.....	19	19	0
Septicemia.....	3	2	1
Puerperal sepsis.....	2	2	0
Traumatic orbital cellulitis.....	3	3	0
Osteomyelitis.....	2	2	0
Otitis.....	3	3	0
.....	1	0	1
.....	14	14	0
.....	5	5	0
Scarlet fever.....	8	8	0
Ludwig's angina.....	2	0	2
Otitis media.....	9	9	0

The clinical results obtained in the treatment of human beings with infections produced by beta hemolytic streptococci have been striking. While our series of patients who have received treatment is not large enough for accurate statistical analysis based on mortality figures, in practically every instance marked clinical improvement in the patient's condition occurred promptly after the administration of para-aminobenzenesulfonamide or its derivatives.

In the group of seventy patients in whom these preparations have been used as therapeutic agents there have been four deaths. The first

death, that of a 57 year old Negro, occurred seven hours after treatment was commenced for a hemolytic streptococcic septicemia of several days' duration. The man was considered to be moribund when treatment was instituted. The two patients ill with Ludwig's angina died twenty hours and about thirty-five hours, respectively, after treatment was commenced. We do not believe that any of these cases represent a failure of the therapeutic agents employed. However, the fourth death in our series occurred in a 4 month old infant ill with peritonitis due to beta hemolytic streptococci who had received adequate therapy for twelve days before death suddenly occurred. This we consider to represent a failure of the specific therapy.

Our observations, both experimental and clinical, on the treatment of streptococcic infections lead us to believe that about forty-eight hours is required before maximum therapeutic effects can be obtained with para-aminobenzenesulfonamide or its derivatives. Because of this time factor we feel that if an infection is considered to be due to hemolytic streptococci treatment should be instituted immediately. Also striking results should not be expected when patients with far advanced infections or those who are moribund are treated.

As a result of our experiences in treating these seventy patients ill with hemolytic streptococcic infections we have been able to formulate certain rules for estimating the amount of drug needed in the treatment of acute infections due to streptococci of this type.

When prontosil, 2.5 per cent solution, is used, the total amount required during the first twenty-four hours of treatment is calculated on the basis of 1 cc. for each pound (0.5 Kg.) of body weight up to 120 pounds (54.4 Kg.). For patients over this weight the first day's dose is 120 cc. The total daily amount is divided into six parts, and a dose is given every four hours by a subcutaneous injection. An example is that of a patient weighing 120 pounds who would receive 120 cc. of prontosil solution during the first twenty-four hours of treatment in six subcutaneous injections of 20 cc. each. Prontosil, 2.5 per cent solution, is rapidly absorbed and should not be administered by the intravenous or intrathecal route.

Prontylin tablets are to be used only for oral administration. The total dose for the first twenty-four hours is calculated on the basis of 3 tablets (1 Gm.) for each 20 pounds (9.1 Kg.) of body weight up to 100 pounds (45.4 Kg.). In the treatment of acute infections we believe that 5 Gm. of this substance represents the maximum daily dose in adults which may be used with safety. This total amount is divided into four doses given at intervals of six hours. Thus, for a patient weighing 100 pounds the total amount required for the first day would be 16 tablets, or 4 tablets every six hours.

Para-aminobenzenesulfonamide is not generally available at the present time, nor is it yet entirely satisfactory for use, because of certain difficulties in its administration. However, during the past few months, in cases of severe infections we have been instituting treatment by giving a hypodermoclysis of para-aminobenzenesulfonamide dissolved in sterile physiologic solution of sodium chloride. This chemical is soluble up to roughly 0.8 per cent in hot physiologic solution of sodium chloride. In the preparation of this substance for clinical use, it is our practice to dissolve 0.8 Gm. in 100 cc. of physiologic solution of sodium chloride which has been brought to the boiling point and then cooled to 90 C.

The solution is then cooled to 37 C. and is given by hypodermoclysis into loose subcutaneous tissue. The amount of chemical given by this method is gaged by the weight of the patient. We use 0.8 Gm. in 100 cc. of physiologic solution of sodium chloride for patients weighing up to 40 pounds (18 Kg.). For those weighing between 40 and 80 pounds (18 and 36 Kg.) the dose is 1.6 Gm. of the chemical in 200 cc. of physiologic solution of sodium chloride. Patients weighing between 80 and 120 pounds (36 and 54.5 Kg.) receive 2.4 Gm. dissolved in 300 cc. of physiologic solution of sodium chloride, while for patients weighing over 120 pounds the dose is 3.2 Gm. of para-aminobenzenesulfonamide dissolved in 400 cc. of physiologic solution of sodium chloride. These solutions are administered soon after preparation because of the tendency of the chemical to crystallize out of solution on standing at temperatures lower than 37 C.

An 0.8 per cent solution of para-aminobenzenesulfonamide in physiologic solution of sodium chloride may also be used intrathecally in the treatment of streptococcic meningitis.⁶ In general, it has been the experience of those who have used para-aminobenzenesulfonamide in this way that little cellular reaction to the chemical has been observed and no toxic manifestations. The general practice in administering para-aminobenzenesulfonamide intrathecally should closely follow that recommended for the use of antimeningococcus serum in meningococcic meningitis, namely, that rather complete spinal drainage by lumbar puncture should be instituted and then from 15 to 25 cc. of a warm, freshly prepared 0.8 per cent solution of para-aminobenzenesulfonamide should be permitted to flow in by gravity. The solution should never be injected under pressure.

As the result of our observations we believe that the following suggestions represent effective amounts of para-aminobenzenesulfonamide or its derivatives during the first twenty-four hours of treatment in streptococcic infections of varying degrees of severity.

6. Schwentker, Francis F.: Personal communication to the authors. Edwards, Lydia: Personal communication to the authors.

In severe infections in which the immediate prognosis is grave, either prontosil, 2.5 per cent solution, or para-aminobenzenesulfonamide in an 0.8 per cent solution in physiologic solution of sodium chloride is given by the parenteral route in the recommended doses. In addition, prontylin tablets in one half of the estimated amount are given orally beginning about four hours after parenteral therapy has been instituted.

In moderately severe infections the patient is given either the estimated amount of prontosil, 2.5 per cent solution, parenterally or prontylin tablets orally during the first twenty-four hours of treatment. The drugs are not used in combination.

Mild or relatively chronic streptococcic infections can be controlled by the use of prontylin tablets alone, and as a rule in infections of little immediate severity from one half to two thirds of the estimated dose will be effective.

The question of the amount of the various chemicals needed after the first day of treatment has been completed is difficult to outline and should depend on the clinical condition of the patient. In cases of severe streptococcic disease it has been our practice to continue treatment on the original basis of the first day until a definite improvement in the condition of the patient has been noted. In the patient in whom a streptococcic septicemia is present we feel that at least two blood cultures should be negative for beta hemolytic streptococci before one starts to decrease the total daily amount of the chemical which is being employed.

In moderately severe streptococcic infections, especially those in which a visible lesion is present, such as erysipelas, peritonsillar abscess and scarlet fever, one must be governed in respect to further treatment entirely by the clinical appearance of the lesions and the general clinical condition of the patient. Rarely does one have to continue the chemical employed in full doses after the second twenty-four hours of treatment. At this point the amount of the drug may, if the clinical condition warrants, be cut by a quarter or a third and then gradually decreased over a period of a week. It should be borne in mind that if the drug is discontinued too soon a recurrence of the streptococcic lesion may occur.

When one is dealing with mild acute streptococcic infections, recovery after the administration of para-aminobenzenesulfonamide or its derivatives is generally so prompt that it seems safe to decrease rapidly the amount of the chemical administered. In mild chronic infections due to beta hemolytic streptococci, such as chronic impetigo and chronic otitis media, it is often necessary to administer the drug over a rather long period or until a definite clinical and bacteriologic cure is effected.

Even so, a recurrence of the infection may occur, but as control is again easily established with these chemicals, one should not be alarmed.

It may be asked, "How long can one administer para-aminobenzenesulfonamide to a patient without any danger?" On this point one can only say that a prolonged clinical experience with the drug will be necessary before the final answer is known. We have observed patients who have been given rather large amounts of para-aminobenzenesulfonamide (from 3 to 5 Gm. per day by mouth) over a period of several weeks without any ill effects.

When the question arises as to which preparation should be selected for use in the treatment of a given patient with hemolytic streptococcic infection, we can answer by saying that for patients who are able to swallow tablets para-aminobenzenesulfonamide given by mouth (in the form of prontosil tablets) is the most satisfactory from the point of view both of results obtained and of ease of administration. With patients who cannot swallow, or who are vomiting, parenteral medication is indicated, and either a solution of para-aminobenzenesulfonamide or the chemical which is marketed under the trade name of prontosil, 2.5 per cent solution, may be used. In this connection, it should be noted that 100 cc. of prontosil solution if completely broken down into the active form will deliver 0.73 Gm. of para-aminobenzenesulfonamide and that therefore one can in a given period reach a higher concentration of the effective principle with para-aminobenzenesulfonamide than with prontosil solution. On the other hand, owing to the difficulties attendant on the parenteral administration of para-aminobenzenesulfonamide, we believe that in most instances prontosil solution is the drug of choice.

It should also be noted that the daily and total dosage of these compounds which we have recommended is in excess of that advised by other observers.⁷ We know, nevertheless, that these doses represent amounts that are rapidly effective. Undoubtedly as more information is gained concerning the use of these compounds in the treatment of streptococcic infections our proposals for dosage will be altered.

TOXICITY

When a new chemotherapeutic compound is being tested for clinical use it is of the utmost importance to observe whether or not the drug itself has any toxic effects on the animal body. In the case of para-aminobenzenesulfonamide and its derivatives, we may say that there is little evidence that these compounds are appreciably toxic for human beings, at least as far as their immediate effects are concerned. The evidences of toxicity which have been observed are the following:

7. Colebrook and Kenny.¹¹ Colebrook and Kenny.¹²

A few patients have complained of nausea, ringing in the ears or slight dizziness shortly after the ingestion of the first oral dose of tablets containing para-aminobenzenesulfonamide. These symptoms pass off rapidly as a rule and have not, so far, contraindicated the use of the compound.

If prontosil, 2.5 per cent solution, is given in a single dose of 100 cc. subcutaneously or in repeated smaller doses, fever may result. Bennett⁸ has noted that normal human beings who receive a single large dose (100 cc.) of prontosil solution by the subcutaneous route exhibit fever within twenty-four hours. We have also noted that the rather prolonged administration of large doses (5 Gm. per day) of tablets containing para-aminobenzenesulfonamide will also produce fever which disappears within twenty-four hours after the drug is discontinued. This toxic manifestation of these compounds is of importance in severe cases of streptococcic infection in which sometimes one's clinical judgment must be carefully exercised in order to differentiate between fever produced by the infection and fever produced by the chemical.

Four patients have exhibited slight cyanosis coupled with rapid breathing while under treatment. These symptoms are the result of acidosis. Jaundice developed in one patient while he was under treatment, and recovery occurred promptly after para-aminobenzenesulfonamide was discontinued. This patient has subsequently been given large doses of this drug without a recurrence of jaundice. The possibility of acute injury to the liver must be borne in mind. Colebrook and Kenny¹⁰ reported that sulfhemoglobinemia developed in three patients while they were under treatment. He wondered whether the use of saline cathartics played a rôle in the production of the condition. None of our patients has received saline cathartics or laxatives, but sulfhemoglobinemia has developed in three.

None of the toxic manifestations which we have observed has been severe. The question of late delayed toxic effects from the use of these compounds can be answered only when our clinical experience with para-aminobenzenesulfonamide is more mature.

CONCLUSIONS

Para-aminobenzenesulfonamide and its derivatives have a specific chemotherapeutic effect in the treatment of infections produced by beta hemolytic streptococci. In our opinion, these chemicals have a low degree of toxicity. It seems logical to believe that the prompt recognition of the nature of hemolytic streptococcic infections plus the adequate administration of the specific chemotherapeutic agents will greatly lessen the dangers inherent in these types of infection.

⁸ Bennett, Stanley H. Personal communication to the authors.

PERTHES' DISEASE

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Fifty-seven cases of Perthes' disease which were roentgenographed and studied in the Hospital for Joint Diseases between 1929 and 1936 formed the basis of this study. The aim of the analysis was to interpret the aberrations as noted on the roentgenograms in the light of current knowledge of pathologic processes in bone.

CLINICAL STATISTICS

The statistical data may be briefly summarized as follows:

1. *Age at Which Symptoms Commenced.*—The distribution of cases according to age was as follows: 3 years, three; 4 years, one; 5 years, nine; 6 years, eleven; 7 years, nine; 8 years, twelve; 9 years, five; 10 years, three; 11 years, none; 12 years, two; 13 years, one, and 14 years, one.

2. *Hip Affected.*—In twenty-eight cases, the right hip was affected; in twenty-six, the left, and in three, both hips.

3. *Sex and Race.*—The male patients numbered 45; the female patients, 12. All were white (from 15 to 20 per cent of the patients received in this hospital are colored).

4. *Trauma.*—This was present in twelve cases.

5. *Interval Between First Trauma and First Visit to Institution.*—This interval was one month in two cases; two months in one; three months in two; four months in two; one year in three; two years in one, and three years in one.

6. *Pertinent Clinical Data.*—Most of the patients complained of a limp or of pain in the affected hip region; some experienced pain in the ipsilateral knee; others were aware only of a dull ache about the hip; a few noted a slight shortening of the limb without accompanying pains.

7. *Physical Findings.*—The physical examinations demonstrated in some of the patients a fixed flexion adduction deformity of the femur in the involved hip joint. Limitation of internal and external rotation

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as well as of flexion, extension, abduction and adduction of the femur was encountered in many.

8. *Measurements.*—One of the procedures in the course of the study was to measure in fractions of an inch the distance (as revealed on the roentgen plate) from the summit of the outer portion of the femoral capital epiphysis to the directly opposed acetabulum. The measurements are given in table 1. Table 1 reveals that with the exception of two instances (excluding also three cases which were bilateral) the distance

TABLE 1—*Distance (in Fractions of an Inch) from Summit of Outer Portion of Capital Epiphysis to Opposed Acetabulum*

Age, Years	Normal Hip	Abnormal Hip
3	6/16 (0.95 cm)	6/16 (0.95 cm)
4	3/16 (0.48 cm.)	6/16 (0.95 cm)
5	4/16 to 6/16 (0.63 to 0.95 cm)	4/16 to 7/16 (0.63 to 1.11 cm)
6	2/16 to 6/16 (0.32 to 0.95 cm)	4/16 to 6/16 (0.63 to 0.95 cm)
7	3/16 to 5/16 (0.48 to 0.80 cm)	4/16 to 7/16 (0.63 to 1.11 cm)
8	4/16 (0.63 cm)	4/16 (0.63 cm)
9	4/16 to 6/16 (0.63 to 0.95 cm)	4/16 to 8/16 (0.63 to 1.27 cm)
10	4/16 to 6/16 (0.63 to 0.95 cm)	2/16 to 4/16 (0.32 to 0.63 cm)
11-14	2/16 to 6/16 (0.32 to 0.95 cm)	2/16 to 6/16 (0.32 to 0.95 cm)

TABLE 2—*Height (in Fractions of Inch) of Outer Portion of Capital Epiphysis*

Age, Years	Normal Hip	Abnormal Hip
3-6	6/16 to 10/16 (0.95 to 1.59 cm)	2/16 to 8/16 (0.32 to 1.27 cm)
7-9	8/16 to 12/16 (1.27 to 1.90 cm)	2/16 to 12/16 (0.32 to 1.90 cm)
10-14	8/16 to 13/16 (0.27 to 2.06 cm)	4/16 to 11/16 (0.63 to 1.74 cm)

TABLE 3—*Width (in Inches) of Upper Epiphysal Cartilage Plate*

Age, Years	Normal Hip	Abnormal Hip
3-6	1 to 1 3/8 (2.54 to 3.48 cm)	1 to 1 3/8 (2.54 to 3.48 cm)
7-9	1 2/8 to 1 7/8 (3.17 to 4.75 cm)	1 1/16 to 2 (2.70 to 5.08 cm)
10-14	1 to 1 7/8 (2.54 to 4.75 cm)	1 to 2 1/4 (2.54 to 5.72 cm)

was greater on the affected side. In two cases the joint space on the involved side was smaller.

Another procedure was to measure the height of the outer portion of the capital epiphysis. The involved side was smaller than the normal one during some phase of the disease. The exact data are given in table 2.

Still another procedure was to measure the width of the upper epiphysal cartilage plate, i. e. the distance from the superior to the inferior cortex of the femoral neck, just at their junction with the capital epiphysis. The findings are recorded in table 3.

The fourth item was the measurement of the length of the superior cortex of the femoral neck, i. e., the distance between the proximal surface of the greater trochanter and the upper femoral epiphysial cartilage plate. The data (table 4) show that extreme shortening of the femoral neck is not a frequent finding in the young.

The last procedure was the determination, by means of a protractor, of the angle formed at the junction of the femoral neck and the shaft. (A line was drawn bisecting the femoral neck; another line was drawn bisecting the upper portion of the femoral shaft.) The obtuse angle was measured where the two lines crossed. The data are given in table 5.

TABLE 4—*Length (in Inches) of Superior Cortex of Femoral Neck*

Age, Years	Normal Hip	Abnormal Hip
3 5	1/2 to 1 1/4 (1 27 to 3 18 cm)	1/2 to 1 1/4 (1 27 to 3 18 cm)
6	3/4 to 1 (1 91 to 2 54 cm)	3/4 to 1 (1 91 to 2 54 cm)
7	1/2 to 1 1/2 (1 27 to 3 81 cm)	1/2 to 1 1/2 (1 27 to 3 81 cm)
8	1/2 to 7/8 (1 27 to 2 22 cm)	1/2 to 7/8 (1 27 to 2 22 cm)
9	5/8 to 6/8 (1 60 to 1 90 cm)	1/2 to 6/8 (1 27 to 1 90 cm)
10	1 to 1 1/8 (2 54 to 2 86 cm)	1 to 1 1/8 (2 54 to 2 86 cm)
11 14	1 to 1 1/2 (2 54 to 3 81 cm)	3/4 to 1 1/2 (1 91 to 2 54 cm)

TABLE 5—*Angle (in Degrees) Formed at Junction of Femoral Neck and Shaft*

Age, Years	Normal Hip	Abnormal Hip
3	150	150
4	135	135
5	135 to 145	135 to 145
6	140 to 150	140 to 150
7	140 to 145	140 to 145
8	135 to 145	135 to 145
9	130 to 140	125 to 135
10	130 to 140	125 to 135
11 14	140 to 150	130 to 150

PATHOLOGY

The second part of this paper relates to the pathologic processes that were probably responsible for the alterations in the configuration of the proximal portion of the femur as noted on the roentgenograms in our fifty-seven cases. This part of the paper will be divided into three sections. The first will deal with the changes in the upper epiphysis of the involved femur.

1. *Changes in the Upper Capital Epiphysis.*—Roentgenographic examination of normal hip joints of children shows that the bony portion of the capital epiphysis is by no means regularly outlined as a hemisphere or as an arc of a circle. We have frequently observed that the outline of the outer portion of the capital epiphysis is slightly taller

than the inner one (fig. 1 *A*). In several instances we have found also that the portion of the normal capital epiphysis situated close to the medial wall of the acetabulum appeared flattened as if compressed by the ligamentum teres.

With this in mind we observed that in the early stages of Perthes' disease the roentgenogram may exhibit only slight flattening of the

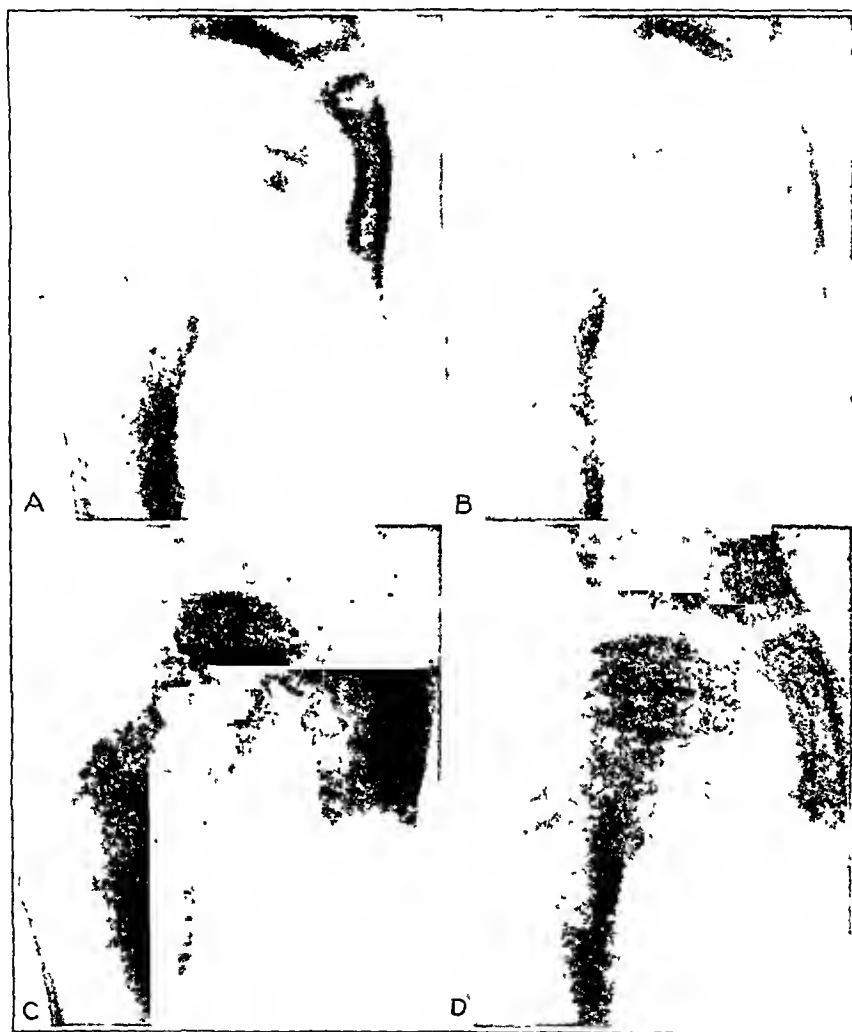


Fig. 1.—*A* shows the taller outer portion of the bony nucleus of the capital epiphysis. *B* discloses slight flattening of the outer portion of the bony nucleus of the capital epiphysis in a boy of 6 years with Perthes' disease in an early stage. Motion in the affected hip is limited. *C* shows definite flattening of the outer portion of the bony nucleus of the capital epiphysis in a boy of 7 years with early Perthes' disease. *D*, taken three months later than *C*, in the same case, shows accentuation of the flattening and an area of cystic rarefaction in the metaphysis.

outer portion of the capital epiphysis (fig. 1 *B*). Concomitantly there is a slight increase in the joint space.¹ This is not the result of separation or dislocation of the femur from the acetabulum. It seems fair to reason by inference that it is due to resorption of the bone with replacement by soft tissue.²

In addition, the density of the capital head, as determined by roentgenogram, may also become modified. However, the density of the region in question may appear normal. This shadow, nevertheless, may be slightly more opaque than the atrophic metaphysial region of the involved femur. It seems to us that the normal density of the

1. The joint space as observed on the roentgenogram is the distance between the subchondral zone (provisional zone of calcification) of the femoral capital epiphysis and that of the roof of the acetabulum.

2. Perthes, G.: Ueber Osteochondritis deformans juvenilis, *Arch. f. klin. Chir.* **101**:779, 1913. Legg, A. T.: Osteochondral Trophopathy of the Hip-Joint, *Surg., Gynec. & Obst.* **22**:307, 1916. Sundt, H.: Malum Coxae Calve-Legg-Perthes, *Zentralbl. f. Chir.* **47**:538, 1920. Sorrel, E.: Six cas d'ostéo-chondrite déformante infantile de l'épiphyse fémorale supérieure, *Rev. d'orthop.* **8**:31, 1921. Kreuter, E.: Zur Actiologie und Pathogenese der Osteochondritis deformans juvenilis (Perthes), *Beitr. z. klin. Chir.* **122**:263, 1921. Waldenstrom, H.: The Definite Form of Coxa Plana, *Acta radiol.* **1**:384, 1922. Vignard: Deux biopsies dans 2 cas d'ostéo-chondrite déformante juvenile, *Arch. franco-belges de chir.* **25**:1088, 1922. Heitzmann, O., and Engel, H.: Epiphysenerkrankungen in Wachstumsalter, *Klin. Wchnschr.* **2**:397 (Feb.) 1923. Jansen, M.: Coxa Plana and Its Causation, *J. Bone & Joint Surg.* **5**:265 (April) 1923. Kirklin, B. R.: Osteochondritis Deformans Juvenilis, *Am. J. Roentgenol.* **10**:701 (Sept.) 1923. McWhorter, G. L.: Operation on Neck of Femur Following Acute Symptoms in a Case of Osteochondritis Deformans Juvenilis Coxae (Perthes' Disease), *Surg., Gynec. & Obst.* **38**:632 (May) 1924. Walter, H.: Zur Histologie der Perthes'schen Krankheit, *München. med. Wchnschr.* **72**:499 (March) 1925. Moller, P. F.: Clinical Observations After Healing of Calve-Perthes' Disease Compared with Final Deformities Left by That Disease and the Bearing of Those Final Deformities on Ultimate Prognosis, *Acta radiol.* **5**:1, 1926. Legg, A. T.: The End Results of Coxa Plana, *J. Bone & Joint Surg.* **9**:26 (Jan.) 1927. Rockemer, K.: Zur Histopathogenese der Perthes'schen Krankheit, an der Hand eines Frühfalles, *Frankfurt. Ztschr. f. Path.* **35**:1, 1927. Zemansky, A. P., Jr.: Pathology and Pathogenesis of Legg-Calve-Perthes' Disease, *Am. J. Surg.* **4**:169, 1928. Lippmann, R. K.: The Pathogenesis of Legg-Calvé-Perthes' Disease Based upon the Pathologic Findings in a Case, *ibid.* **6**:785 (June) 1929. Freund, E.: Zur Deutung des Röntgenbildes der Perthes'schen Krankheit, *Fortschr. a. d. Geb. d. Röntgenstrahlen* **42**:435 (Oct.) 1930. Lang, F. J.: Osteo-Arthritis Deformans Contrasted with Osteo-Arthritis Deformans Juvenilis, *J. Bone & Joint Surg.* **14**:563 (July) 1932. Cage, H. C.: A Possible Early Sign of Perthes' Disease, *Brit. J. Radiol.* **6**:295 (May) 1933. Freund, E.: Active and Passive Pleat Formation of Joint Cartilage, *Arch. Path.* **18**:186 (Aug.) 1934. King, E. S. J.: Localized Rarefying Conditions of Bone, Baltimore, William Wood & Company, 1935. Brailsford, J. F.: The Radiology of Bones and Joints, Baltimore, William Wood & Company, 1935. Eyre-Brook, A. L.: Osteochondritis Deformans Coxae Juvenilis or Perthes' Disease, *Brit. J. Surg.* **24**:166 (July) 1936.

capital epiphysis may reflect either partially or totally necrotic bone. We do know that unresorbed necrotic bone may give a normal roentgenographic picture.³

However, at varying intervals from the incipency of symptoms the roentgenographic density of part or most of the head may alter. The shadow cast may appear similar to that of dense sclerotic bone. In one particular instance this was observed after two months (fig. 2). Exaggerated opacity of this region is probably dependent on the presence of newly formed living bone about, and the partial compression of, the original necrotic bone trabeculae. When these two conditions are absent, the density of the shadow is normal.

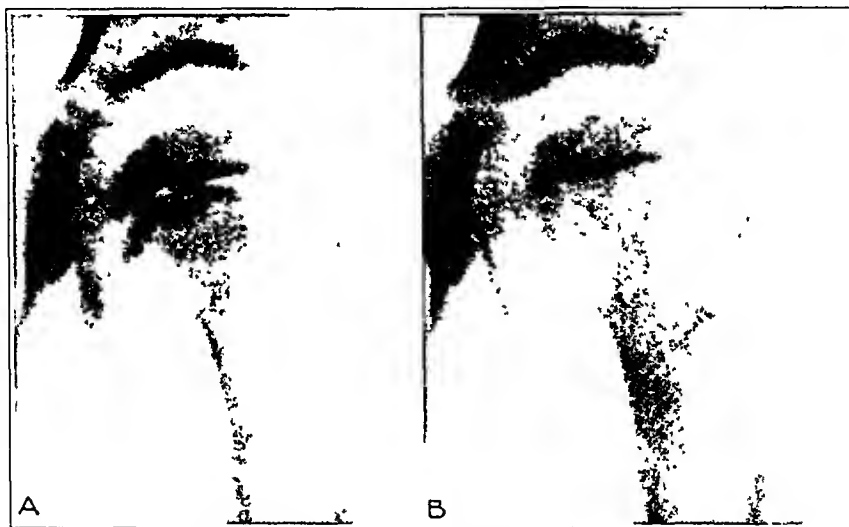


Fig. 2.—*A* shows early changes of Perthes' disease in a boy of 5 years; *B*, the increasing density of the femoral head two months later.

It is of interest to mention here that specimens of the femoral head removed because of nonunion of the fractured femoral neck, in adults, showed on histologic and roentgenologic examination that when new bone formed about the original unresorbed necrotic trabeculae the roentgenographic picture displayed an absolute increase in the density (opacity) of the femoral head. However, should the process of resorption of the original bone keep pace with new bone formation, absolute sclerosis as evidenced roentgenographically may not appear. On the same basis, if resorption continues without the building of new bone, rarefaction (atrophy) will be observed on the roentgenographic film. Sclerosis should in any case not be considered the result only of

3. Jaffe, H. L., and Pomeranz, M. M.: Changes in Bones of Extremities Amputated Because of Arteriovascular Disease, *Arch. Surg.* **29**:566 (Oct.) 1934.

mechanical compression of the trabeculae. Actual compression of trabeculae has, however, been observed microscopically in cases of severe osteoporosis, in cases of long-standing arthritis with secondary subchondral cyst formation and in cases of slipping of the capital epiphysis.

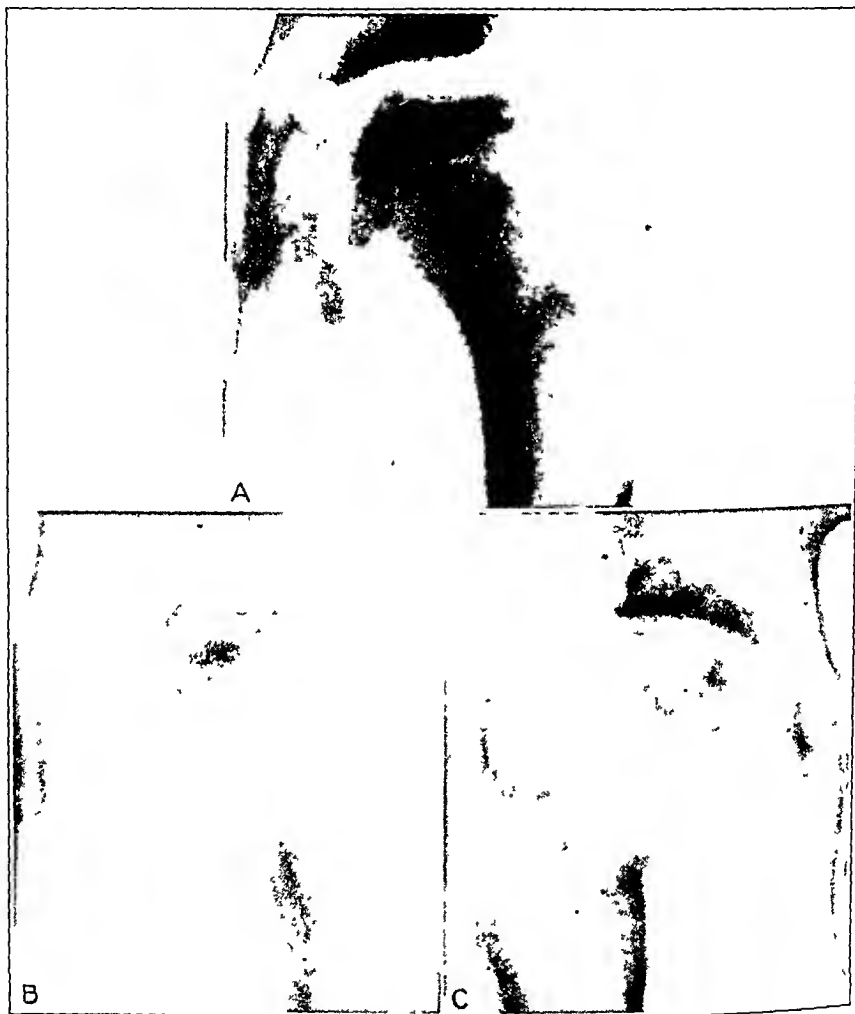


Fig. 3.—*A* shows extreme sclerosis of the femoral head and resorption of the outer portion. *B*, which presents a later stage of the condition shown in *A*, reveals rarefaction of the metaphyseal zone. *C*, taken in another case, shows extreme flattening and irregularity of the bony portion of the femoral epiphysis.

With active resorption of the original femoral epiphysis, the roentgenogram may exhibit constant gradual diminution in the shadow representing the bony elements (fig. 3). In addition, the film may disclose islands of sclerotic bone with neighboring areas of rarefied

bone or no bone (fragmentation, fig. 4). This appearance has been caused probably by local variations in the degree of resorption and production of bone. Occasionally the films present relatively opaque shadows of triangular-shaped pieces of bone (sequestrums?) located approximately in the region where the ligamentum teres inserts into the femoral head (fig. 5). Such areas of increased density may be the result of production of new bone and of compression of some of the original trabeculae. The round ligament may provide enough blood channels to induce building of new bone.

In roentgenograms, even in many of those made soon after the onset of symptoms, bone can be seen extending from the femoral capital epiphysis laterally beyond the limits of the roof of the acetabulum. It

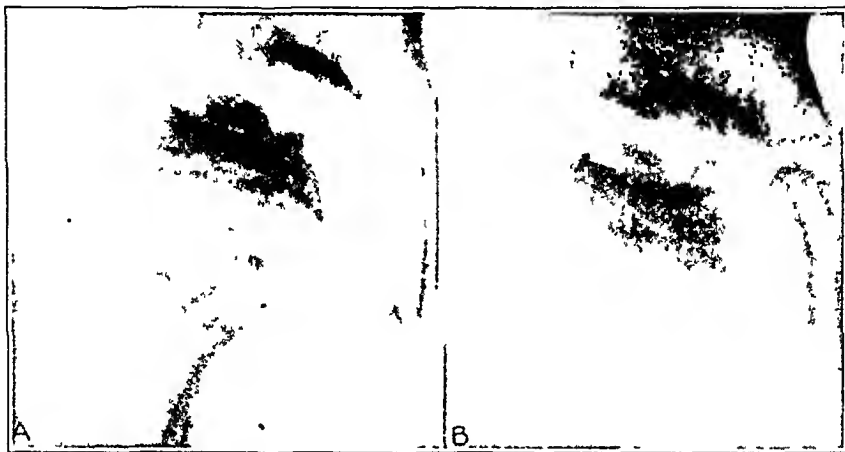


Fig. 4.—*A* shows a shadow appearing as an island of dense bone. *B*, taken three months later, shows diminution in the density of this shadow following the application of a plaster of paris spica. Note the irregularities in the contour of the acetabular roof.

may appear as a ledge of bone extending over the metaphysis (fig. 5). Usually the bone in question is not sclerotic. It is more than likely that it has not formed in consequence of mechanical compression, i. e., extrusion. It is known that, especially in the young, there is good blood supply in the region where the periosteum of the femoral neck meets the articular cartilage. Here, also, osteogenesis may be provoked by abnormal irritation of the tissue. It is probably in this area that new bone forms in conjunction with either rarefaction or condensation of the outer portions of the capital epiphysis.

With progressive resorption, the femoral epiphysis may be so reduced as to appear wafer-like roentgenographically. In a few cases we noted that practically all the bone was resorbed. In the majority

of instances the width of the translucent zone (joint space) appeared increased. The greater trochanter of the involved femur may be at the same height as its mate or it may be a trifle higher if adduction of the involved femur is absent. This indicates further that the translucent zone (joint space) may be occupied by soft tissue. In two cases



Fig. 5.—*A* reveals a sclerotic zone in the femoral epiphysis of a 6 year old girl. She had limped for four months. Note the flattening of the femoral epiphysis and the "beaking" of the outer portion. *B*, taken four months later, shows almost complete disappearance (resorption) of the sclerotic zone. Note the flattening of the caput and the pronounced "beaking" of the outer portion. *C*, taken eight months later than *B*, reveals increasing sclerosis of the femoral head (healing), "beaking" of the femoral head and widening of the femoral neck. Note that the neck appears short, but that this is not a coxa vara deformity.

in our series the width of the translucent zone was less than normal; the greater trochanter was elevated above its normal site, causing an actual shortening of the limb.

The changes described do not reach the same proportion in all cases, nor is there any regularity in their progression. In some the resorptive phenomena may be mild; in others, quite severe. There is no definite



Fig. 6—A shows early changes of Perthes' disease in a boy 7½ years old. Note the sclerosis and flattening of the head. B, taken after six months of immobilization, shows a diminution of the area of sclerosis. C, taken nine months after B, exhibits almost complete disappearance of the sclerosis in the femoral head. D shows the end-result in another case after immobilization of the hip in a brace for eighteen months. Note the smooth contour and uniform sclerosis of the femoral head.

plan, and there are minor variations. Each patient has his own characteristic transformations. In those in whom bone dissolution is at a minimum and the shape of the epiphysis has not been markedly remodeled, the sclerosis of the head may disappear in from six to eighteen months (fig. 6 *A*, *B* and *C*). In some cases complete transformation of the pathologic head to one with some semblance of nor-



- Fig. 7.—*A* shows the hip of a patient with Perthes' disease, taken six months after the onset of symptoms. *B*, taken seven years after *A*, reveals secondary hypertrophic osteo-arthritis. Note the enlargement of the femoral head, the narrowing of the joint space, the rarefactions in the femoral head, the shortening of the femoral neck. *C* shows the hip of another patient. Note in particular a defined area of rarefaction in the metaphysis.

mality has been observed to occur within sixteen months; in others, the period has varied from one to four years (fig. 6 D). Usually, the affected femoral head is wider, owing to the amalgamation of the bone previously formed in the outer portion of the femoral head with that of the epiphysis. Part of the head may extend over the femoral neck and almost reach the tip of the greater trochanter. The flattened femoral epiphysis may also be restored approximately to its normal height.

In most instances, the femoral head even years after the onset of Perthes' disease contains areas of bone of different densities. This indicates probably incomplete realignment and transformation of the old and newly formed bone. There may be roentgenographic evidence of arthritis with single or multiple subchondral cysts. This is often seen in adults who have had either recognized or unrecognized symptoms and signs of Perthes' disease (fig. 7 A and B).

2. *Changes in the Femoral Neck.*—With the early alterations in the femoral capital epiphysis, there may be concomitant generalized rarefaction or atrophy of the metaphyseal zone. This is usually the result of disuse. The region of the epiphyseal cartilage plate may also lose its normal opacity. In some, instead of generalized atrophy, clear-cut single or multiple areas of rarefaction are seen just beneath the region of the epiphyseal cartilage (fig. 7 C). They may make their appearance early in the disease or several months after the onset. These cystlike shadows may at a later date be lined or delimited by dense bone trabeculae (fig. 8). Even in patients showing healing or formation of new bone in the femoral capital epiphysis such rarefactions in the femoral neck demarcated by thick trabeculae were observed. Some were situated from 0.5 to 1.5 cm. distal to the epiphyseal cartilage plate. These cystlike spaces may have the roentgenographic appearance of abscess cavities.

The cystic spaces in the femoral neck are not the result solely of atrophy from disuse. These changes most likely represent local cessation of endochondral ossification of the epiphyseal cartilage plate plus resorption of the existing bone trabeculae. Fibrous tissue invasion of the cartilage plate of the metaphysis is the causative factor of the alterations.⁴ Involvement of the epiphyseal cartilage plate in the early years of life may result in a coxa vara deformity.

4. Delitala, E.: Contribution for the Study of a Typical Disease of the Upper End of the Femur (Perthes' Disease), *Am. J. Orthop. Surg.* **12**:555 (April) 1915. Lang, F. J.: Mikroskopische Befunde bei juveniler Arthritis deformans nebst vergleichenden Untersuchungen über die Femurkopfepiphyse mit besonderer Berücksichtigung der Fovea, *Virchows Arch. f. path. Anat.* **239**:76, 1922. Platt, H.: Pseudo-Coxalgia: A Clinical and Radiographic Study, *Brit. J. Surg.* **9**:366, 1922.



Fig. 8.—*A* (case of F. H., aged 6 years) reveals sclerosis of the flattened head and thickening of some of the trabeculae in the metaphysis. The latter condition produces a shadow resembling a cyst. The roentgenogram was taken thirteen weeks after the onset of symptoms. *B* (case of S. M., aged 6 years) shows a sclerotic flattened head and a cyst in the metaphysis. Compare with the normal mate (*C*). *D* (case of A. W.) reveals changes in the femoral head and circumscribed rarefied areas in the metaphysis.

In addition, the superior cortex of the femoral neck may also undergo pathologic transformation. This cortex (normally thinner than the inferior one) may become rarefied or may show evidences of periostitis (fig. 9 *A*). When the femoral capital epiphysis widens and extends over the metaphysial zone, new bone forms on the superior cortex of the femoral neck in order to support this accessory portion of



Fig. 9.—*A* (case of S. D., aged 12 years) shows irregularity in the contour of the femoral head, narrowing of the joint space and periostitis of the superior cortex of the neck. *B* (case of C. D., aged 10 years) exhibits changes in the caput and metaphysis. (The femur is in adduction and flexion.) There is an apparent increase in the joint space between the inner surface of the femoral head and the acetabulum.

the head. This accounts for the widening of the femoral neck as observed in Perthes' disease. (It is important to recognize that a normal femur in flexion or in external rotation may give a roentgenographic shadow which displays some widening and shortening of the femoral neck.)



Fig. 10.—*A* shows a case of Perthes' disease. *B* shows insertion of a hollow drill through the femoral neck and part of the head. *C*, taken four months after drilling, discloses the channel formed by the drill. *D*, taken two and one-half years after drilling, reveals especially the foreshortened femoral neck.

3. *Changes in the Acetabulum.*—Because of the deformity in one hip, there exists usually asymmetry of the right and left halves of the pelvic bones. This was recognized on the roentgenogram by the inequality in size of the obturator foraminae. Consequently, the roentgenogram of the involved limb showed in many cases irregularity in the configuration of the "tear drop." There was also an appearance of flaring of the inner acetabular wall (fig. 9 B). In addition, on the



Fig. 11.—Reduced congenital dislocation of left hip. Note the contour of the left femoral head and the irregular configuration of the roof of the left acetabulum.

affected side the distance between the medial surface of the involved femoral head (even when an adduction deformity was absent) and the inner acetabular wall was increased. In a few patients, atrophy of the roof of the acetabulum, and in older ones, sclerosis, was observed. In several, irregularities in the contour of the extreme tip of the roof of the acetabulum (spur formation) were encountered, while in still others the inner acetabular wall was irregular and flared medially.

SUMMARY AND CONCLUSIONS

An analysis was made in an attempt to interpret the roentgenographic appearances observed in Perthes' disease in the light of modern pathology. Of special interest were the discrete pseudocystic areas in the femoral neck. These were believed to have resulted from, or been directly caused by, fibrous invasion or temporary cessation of growth of part, or of the whole, of the epiphysial cartilage plate. Interference with the growth of this plate can also follow surgical intervention, such as drilling or pegging of the femoral neck (fig. 10).

In this study we noted that reduced congenital dislocation of the hip as well as healed syphilitic osteochondritis or Morquio's disease may in certain cases at first hand simulate Perthes' disease roentgenographically (fig. 11). However, we observed in several cases of the first-named condition that the entire femoral capital epiphysis was usually flattened, with the medial half involved to a greater degree (the reverse of Perthes' disease).⁵ In the cases of syphilitic osteochondritis and of Morquio's disease concomitant lesions existed in other bones.

As for the etiology of Perthes' disease, the roentgenographic and pathologic observations shed little light. However, the changes observed in the femoral epiphysis and metaphysis may to a certain degree be comparable to those occurring in bones involved by acute traumatic necrosis—for example, those following sprains of the knee, ankle, elbow or wrist.

Dr. H. L. Jaffe gave many helpful criticisms.

5. Mayr, O.: Ueber Ossifikationsstörungen vor und während der Luxationsbehandlung, *Ztschr. f. orthop. Chir.* **61**:66, 1934. Marottolo, O.: Malattia di Perthes e sublussazione congenita dell'anca, *Chir. d. org. di movimento* **20**:161, 1934.

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THE DECLINE IN THE STRENGTH OF CATGUT AFTER EXPOSURE TO LIVING TISSUES

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It was largely through the efforts of Philip Syng Physick (1816), the first professor of surgery in the School of Medicine of the University of Pennsylvania, that catgut came into general use. He carried out experiments with a wide variety of suture materials and demonstrated the absorbability of catgut. It remained for Lister (1868), however, to begin experiments on the sterilization of catgut, a study which he continued for forty years.

The main requirements for good surgical catgut have been sterility, strength, suppleness and absorbability. The great bulk of the experimental work on catgut recorded in the medical literature has been concerned with its sterility and the effect of various methods of sterilization on its tensile strength. Suppleness is largely a matter of clinical opinion, but it has also been studied in the laboratory by determining the loss of tensile strength that results from knotting.

The absorbability of catgut was demonstrated by Physick in 1816 by placing catgut in contact with ulcers so that it was exposed to the purulent secretions of the wound until it dissolved. The first studies of its absorbability in animals were made by Porta (1845), who used dogs, horses and sheep for his experiments. He buried catgut in eighty instances and classified his results according to the duration of the experiments. In thirty-three experiments the catgut was absorbed in from one day to three years. Although the period necessary was often long, he concluded that catgut was absorbed more readily than other materials then being used for suture and ligation.

Lister made numerous scholarly contributions to this subject. He was chiefly concerned with the sterilization of catgut, its fate in tissues,

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the effect of infected serum on it, the effect of serum on its tensile strength and, later, the effect of chromicizing on its absorbability.

His studies on its fate in tissues showed that it was not only absorbed but replaced with granulation tissue and ultimately with a band of scar tissue (1868). While he measured the tensile strength of catgut prepared by various methods and determined the effect of serum on the tensile strength, he apparently never studied tensile strength during the process of absorption.

Cumming (1872) tied the carotid artery of a rabbit with heavy phenolized catgut and killed the animal after thirty-three days. He found the strands nearly replaced by fibrous tissue. In 1873 von Fillenbaum reported the use of phenolized catgut in the suture of a wound of the hand. The ends came away in four days with filaments of the buried portions. He ligated the carotid artery of a large dog with catgut and found that after fourteen days the ligature was entirely absorbed except for a few microscopic traces. He believed that catgut was fully absorbed in tissues.

Callender (1874) examined a femoral artery nineteen days after ligation with phenolized catgut and found that the ligature had been absorbed. He also placed a number of samples of catgut in a pocket-shaped wound that had resulted from the removal of a fatty tumor on a patient's back. Both ends of each sample were left outside the wound, and a sample was removed every two or three hours and examined. The experiments were not begun until four days after operation, and the secretions from the wound were ordinary and "at no time fetid." After twenty-four hours of contact with the wound, the specimens were found to be thinned. In from forty to forty-five hours only a thin thread remained, and in from fifty-five to sixty hours all had given way. Distilled water at 98 F. produced scarcely any change in one hundred hours. Bruns (1875) placed ligatures of no. 1 catgut on large vessels in thirteen dogs and examined them after ten, twenty, thirty and forty days. At the end of ten days the catgut in four instances was still present but was narrowed. At the end of twenty days only half a loop could be identified macroscopically; after the thirty and forty day periods only microscopic traces remained, except for a fine thread seen macroscopically in one of the four animals kept forty days. Bruns did the first controlled work on the effect of infection of the wound on catgut.

Eliaschewitsch (1875) found that catgut disappeared in thirty days after it was placed in the tissues of the dog's back. Fine phenolized catgut became attenuated in from five to six days or less. Güterbock (1875) placed catgut in the achilles tendons of white rats and kittens and found it microscopically after fourteen days, when it was no longer visible macroscopically. Murinoff (1875) placed several kinds of catgut

in the horns of the uteri of kittens and dogs. No. 3 catgut (Lister's) was absorbed in from twenty to thirty days, though the knots persisted from twenty-five to seventy days. He noted that the catgut was swollen and weak after seven days. Fleming (1876) studied the microscopic changes in catgut inserted in the backs of dogs and rabbits. He found that the strands were completely invaded with cells in from five to twenty days and that granulation tissue was subsequently formed.

Mayer (1878) made microscopic studies of catgut incubated in serum (changed as often as it grew cloudy) and reported that absorption was incomplete in thirty-two days. In bile from the gallbladder of man catgut persisted over nineteen months with little change. Mayer also studied catgut in urine, in wounds, embedded in the liver and in tendons. In tendons he noted that catgut often became encapsulated before absorption was complete.

Tillmanns (1879), working on the absorption of various foreign bodies, noted that a sample of middle-sized catgut on a necrotic piece of tissue in the peritoneal cavity became unrecognizable in eight days.

Hallwachs (1879) reviewed the work on the absorbability of catgut that had been published up to the time his paper was written and reported the results of experiments on dogs. He reported that Schuchardt (a dissertation published in Berlin, 1872) buried rather fine English catgut under the skin covering the backs of guinea-pigs. After eleven days he found no trace of it under a magnification of 275 diameters. No trace of a ligature placed on a femoral artery could be found after forty-three days. Hallwachs also referred to a dissertation by Reverdin (Berlin, 1874), in which was reported the use of catgut (Lister's middle-sized) in kittens as an abdominal ligature, with no change after one day. After three and one-fourth days heavy catgut placed in the abdomen was intact, but fine catgut could not be found. After nine days catgut was encapsulated by adhesions. After ten days the outer part was found to be undergoing organization. Catgut examined after fifteen days was encapsulated and the outer part weakened. After nineteen days three fine and two thick pieces could not be found. After twenty-nine days two pieces of catgut of medium thickness were found encapsulated. Evidently Reverdin's results were not uniform.

Hallwachs himself placed catgut and silk in the peritoneal cavities of dogs. After six months he found the catgut replaced with well vascularized connective tissue.

Rosenberger (1880) published a series of interesting experiments on the power of animals to absorb foreign organic material. One of his dogs absorbed a kitten's kidney (fixed in absolute alcohol) from the peritoneal cavity in thirty days.

Macewen (1881), who was one of the first to recommend chromicizing catgut, tested its absorbability by using it as a deep suture in

thirty-one instances and noting the date of softening by making traction on the ends. The amount of traction was not stated. The average time of softening was fourteen days, the earliest being nine days and the longest nineteen days. In another series of experiments the strands were left until the ends dropped off, which occurred in from fifteen to twenty-four days, the average being twenty days. In the same year Lister published his method of chromicizing catgut. He found that the new product was not eroded in a human patient in ten days. In thirteen days erosion had begun. Von Lesser (1884) tested heavy phenolized catgut in kittens and frogs in various sites (e. g., the vessels, the trachea and the subsynovial and subperiosteal spaces). In the crural muscles of kittens he found traces of catgut in granulation tissue after eighty-five days. He also made numerous studies in vitro. Thomson (1889) tested phenolized and chromicized catgut in the uteri and the abdominal walls of kittens, cats and dogs. The phenolized catgut was entirely absorbed in seventeen days. The chromic catgut was intact

TABLE 1.—*Results of Booth on Tensile Strength of Catgut*

Method of Preparation	Days in Tissue				
	0	1	2	3	6
Reverdin (plain).....	14 lb. (6.4 Kg.)	13 lb. (5.9 Kg.)	10 $\frac{1}{4}$ lb. (4.7 Kg.)	8 $\frac{1}{4}$ lb. (3.7 Kg.)	5 $\frac{1}{4}$ lb. (2.4 Kg.)
Chromicized.....	9 $\frac{1}{4}$ lb. (4.3 Kg.)	9 $\frac{1}{2}$ lb. (4.3 Kg.)	9 $\frac{1}{2}$ lb. (4.3 Kg.)	9 lb. (4.1 Kg.)	8 lb. (3.6 Kg.)

after sixty-four days. Silk, he stated, was mostly absorbed at the end of this period. Monari (1890) performed eighty experiments, lasting from thirteen to thirty-four days, on the muscles, subcutaneous tissues and abdominal cavities of rabbits. In none of the tests was the catgut absorbed. The work was said to have been repeated with dogs.

In 1890 Brunner reviewed the whole subject of catgut from the point of view of its sterilization, its strength before use and its absorption. He included reports on clinical experience with catgut from representative clinics all over Germany. It remained for Booth (1894) to test the effect of implantation in tissues on the tensile strength of catgut. The tests were made with a slow, continuous strain testing machine. The samples were knotted. The implantations were made in the lumbar muscles of dogs six days, three days, two days and one day before the animal was killed and the specimens removed. The results, which the author stated should be considered as relative, are partially presented in table 1. This was the first quantitative demonstration that chromic catgut retained its tensile strength longer than the plain variety.

Hofmeister (1896) tested catgut prepared by his method of sterilization with formaldehyde in the subcutaneous tissues of kittens. He

made both macroscopic and microscopic studies and found that the catgut weakened in sixteen days and broke into bits surrounded by connective tissue in from five to six weeks. Catgut prepared with mercury bichloride underwent similar changes.

Borden in 1897 inserted catgut as a skin suture in a convict. The wound suppurated and opened after four days, at which time the catgut (prepared by boiling one and one-half hours in a 1:500 solution of mercury bichloride in alcohol) was found in good condition, with leukocytes only at the edge. In 1898 Thomalla suggested coating catgut with formaldehydized gelatin. He stated that this prolonged absorption, which never occurred in less than from eight to ten days.

In 1899 Minervini reported the results of experiments on the sterility of catgut and the effect on its tensile strength of many processes suggested for its sterilization. These studies particularly emphasized that heat in the presence of moisture reduced the tensile strength of catgut. He investigated the absorption of no. 2 catgut in the peritoneum of dogs and found that traces of the specimens could be found microscopically after one hundred and twenty-five days. Catgut prepared by dry heat, oil of juniper and formaldehyde tended to be absorbed. Catgut prepared with chromic acid and with mercury bichloride tended to become encapsulated. His tests of the tensile strength were made with a weight dynamometer, the strain being increased by 25 Gm. increments. All samples tested were 5 cm. long, and his data represent averages of six determinations.

It was in 1902 that Claudius introduced iodized catgut. He found that as a skin suture it became fully organized, i. e., replaced, in from twelve to sixteen days, which he considered slightly slower than was the case with catgut prepared with phenol and alcohol.

Binney (1904) reported favorable clinical experiences with iodized catgut and stated that it had been found from experiments on rabbits and a few clinical tests that its absorption time corresponded closely with that of plain catgut. He stated further that chromicized catgut could be sterilized by the iodine method.

Miyake (1904) prolonged the absorption time of catgut with an extract of quebracho (an Argentine oak particularly rich in tannic acid). He expressed the belief that ordinary catgut (even up to size 4) keeps its strength only from nine to twelve days. After catgut was soaked for twenty-four hours in 5 per cent solution of this extract it was found to last intact sixty-five days or more in the dog under aseptic conditions but to be absorbed in thirty-two days in a septic wound. It was fully absorbed in from eighty-three to ninety-nine days in clean wounds.

Barling (1905) used iodized catgut as a skin suture and noted absorption in from six to fourteen days, depending on the size employed. Kuhn and Rössler (1908) studied the reaction in the antero-

chamber of the eyes of kittens to iodized and silverized catgut. They tested these and other materials in the skin of man. The samples were removed in eight days. One of the iodized specimens was broken and another thinned in this period, but the majority were less changed.

Ilyin (1908) determined the time of absorption of catgut in different tissues and found absorption to be most rapid in the superficial layers of the skin. Hutchings (1911) conducted tests on no. 2 catgut in guinea-pigs and reported absorption in nine days.

In 1912 Claudius reported a method for simultaneously iodizing and chromicizing catgut by adding 1 per cent potassium bichromate to the iodine and potassium iodide solution used for sterilization. He found that this process did not change the physical characteristics of the catgut, at least not for six months, whereas free chromic acid made it brittle. Two weeks in the combined solution increased the digestion time of no. 2 catgut in 1 per cent pepsin and 1 per cent hydrochloric acid at 37 C. from six to seventeen hours. In animal experiments no. 2 catgut prepared for one week in this solution lasted twice as long as plain dry sterilized or plain iodized catgut. He stated that he had found this to be true in different animal tissues, including the anterior chamber of the eye of the kitten. He stated that catgut prepared this way retained its full strength for five years in tubes.

Callam (1912) made the interesting observation that absorption of catgut in the subcutaneous tissues on the backs of white mice could be slowed by painting the overlying skin with croton oil. The effect could not be demonstrated in guinea-pigs. Berryhill (1913) emphasized the point that the persistence of catgut could be varied by the extent of the chromicizing so that the catgut would last from ten to sixty days in the muscles of the thighs of rabbits. Phillips (1914) implanted catgut prepared by cumene and by the Bartlett process in Belgian hares and small dogs. The absorption time in days is given in table 2. The results of tests of the tensile strength during the periods of absorption were reported in a few cases, but the tests were not complete. This work was published as a preliminary report, but no subsequent report has been found.

Goris and Rolland (1917) studied the rate of absorption of catgut by the rate of invasion by leukocytes. Chromic catgut was sixth most resistant of the nine varieties tested. Iodized catgut was ninth, i. e., the least resistant to the invasion of leukocytes.

In 1929 the entire subject of surgical catgut was reviewed by Bulloch, Lampitt and Bushill. They reported a large amount of original work on the sterilization of catgut, showing that many of the methods proposed were inadequate. They also made extensive studies on the influence of various physical and chemical constants, such as the pH

of the wash liquors and the number of twists per inch of the catgut ligatures, on the tensile strength of the finished product. They did not study the effect of tissue juices on the tensile strength of the catgut.

Howes (1928) studied the decline in tensile strength of Davis and Geck catgut (sizes 00, 0, 1 and 2; types, plain, ten day chromic and twenty day chromic) implanted in dogs in the wall of the stomach. A standard thread-testing machine was used, which was accurate to within one-half pound. The results were recorded as graphs, tensile strengths being plotted against time. The initial strengths were the average of six determinations. The results were represented by straight lines. Tensile strength reached zero in from three to five days for plain catgut, in from seven and a half to thirteen days for the ten day catgut and in from eighteen to twenty-two and a half days for the twenty day catgut. Studies were also reported on the influence of

TABLE 2.—*Absorption Time of Catgut as Ascertained by Phillips*

Plain			Iodized Chromic		
No.	Tissue	Days	No.	Tissue	Days
00	Human prepuce.....	7	1	Peritoneum.....	18
0	Muscle.....	11	1	Muscle.....	22
0	Fascia.....	10	1	Fascia.....	20
1	Muscle.....	13	2	Muscle.....	20
2	Muscle.....	16	3	Muscle.....	20
3	Fascia.....	21			

saline solution, of blood serum, of infected blood serum and of sterile pus on catgut in vitro and on the fate of catgut in infected wounds.

In an interesting series of articles Howes and his co-workers (1929 and 1933) presented the results of studies of the tensile strength of wounds during the course of their healing, of the holding power of sutures in various tissues and of the time of healing of wounds in the stomach sutured with catgut and silk and correlated the results of the studies.

Reil (1928), who has written chiefly on the chemistry of catgut and the chemical reactions that occur in the course of various methods of sterilization, stated that large animals absorb a given amount of catgut faster than small ones. Braun (1929) stated that the fixed cells and leukocytes are more active in the process of absorption than the blood, as shown by experiments in which catgut was placed in the blood stream. Details of the work were not given. Baisch (1930) made a report on the use of copper catgut (developed by von Linden), which he stated remains strong in tissues for eight days and then slowly disappears. He reported a series of five hundred laparotomies and three

hundred vaginal operations in which it had been employed without rupture of the wound.

Mehnert (1930) reported a series of experiments on the persistence of catgut knots in defibrinated human serum. He also introduced catgut in man as a skin suture. Fine no. 000, no. 00 and no. 0 unhardened iodized catgut (Pfrimmer) lost its continuity in from eight to fourteen days. Hühne (1931) stressed the point that absorbability does not parallel holding strength. He placed great emphasis on the amount which catgut swells with moisture, stating that it tends to shorten when it swells. He regarded this as an important cause of its breaking. Accordingly, he recommended catgut sterilized with methyl violet and malachite green in oil, which swells much less than most varieties. After fourteen days the knot of such catgut is still intact, whereas he found the knot loose in the case of iodized gut and entirely gone in the case of plain catgut. He stated that fully iodized catgut requires from three to four weeks for organization and that the knots of the larger sizes may require from three to four months. The time required for organization differs widely with the vascularity of the part. This article contains some of the best photomicrographic reproductions of catgut in the process of absorption to be found in the literature.

In 1933 von Haefen made histologic studies on the absorption of iodized catgut in the muscles of the backs and in the subcutaneous tissues of kittens and came to the conclusion also that absorption was very slow. Still more recently Kraissl and Meleney (1934) proposed a method of testing the resistance of catgut to absorption *in vitro*. Under a strain produced by a 20 Gm. weight the ligature is incubated in 2 per cent solution of trypsin at p_H of 8, and the time required for it to break is measured. This is somewhat similar to the pepsin and hydrochloric acid digestion method used by Claudius in some of his experiments.

Nearly all the investigations of the absorbability of catgut have been either gross determinations of its presence or of its continuity in tissues or histologic studies of various phases of its persistence in tissues. Only Booth (1894), Phillips (1914), Howe (1928) and Kraissl and Meleney (1934) studied the absorption of catgut in terms of its tensile strength. None of these authors reported results with iodized catgut, though Phillips stated that his preliminary results with the catgut prepared by the Bartlett process were similar to those he reported with material prepared with cumene.

A number of authors, e. g., von Fillenbaum (1873), Callender (1874), Bruns (1875), Macewen (1881) and Borden (1897), studied the absorption of catgut in human tissues, but we have been unable to

find any studies on the effect of human tissue fluids on the tensile strength of the catgut.

Our interest in this subject has grown out of recent surveys of the incidence of rupture of the wound in the general surgical services at the Hospital of the University of Pennsylvania (Eliason and McLaughlin [1934] and Lewis [1934]). While the incidence was low, the mortality was considerable, and the complication was associated with eleven deaths in the periods covered by the surveys (about twelve years). Sokolov (1932) recently reviewed the literature on this subject. He estimated the incidence at from 2 to 3 per cent, which was somewhat higher than was found here.

The possible causes of this catastrophe are many, but perhaps the one most frequently imputed is premature weakening of catgut sutures. The relation of catgut to rupture of the wound has been suggested recently by Kennedy (1934), whose article would lead one to believe that rupture can be entirely avoided by using through and through nonabsorbable sutures, such as silkworm gut. It is also suggested by the occasional occurrence of two or three ruptures in close succession during the use of one lot of catgut and by the fact that in doing a secondary closure it is sometimes impossible to find any trace of the catgut originally used. The experience of investigators in retrieving sutures buried in the rectus muscles of dogs suggests another explanation of this sudden disappearance, namely, that the sutures become so surrounded with newly formed tissue that they escape observation. We have spent as long as ten minutes searching through a circumscribed area in a dog only to find a suture after shredding a considerable amount of tissue.

EXPERIMENTS

In order to see if there were any important differences in the rate at which the various kinds of catgut in use at the Hospital of the University of Pennsylvania lost their strength, a considerable number of samples have been tested after varying periods, during which they were implanted in animal tissues and thus subjected to the influence of the tissue fluids. In all, nearly a thousand tests of tensile strength have been made.

The most direct method of estimating the value of a given type of catgut for surgical use is to study it in the human patient and preferably in an abdominal wound. However, as the number of suitable patients available for this purpose is necessarily somewhat limited, preliminary experiments were done on dogs. Most of these were conducted by a technic that would be directly applicable to patients.

Before an attempt was made to compare the decline in tensile strength of different types of catgut, the variations between samples of unused catgut were investigated. All the determinations of the tensile strength were made with a modification of a Bureau of Standards thread-testing machine (fig. 1). By turning the crank at the lower left side, a strand of catgut held in the jaws of the machine is put under tension which is measured on the scale. The weight is moved along

the beam by the crank at the upper right side, which acts through a pair of gears at the fulcrum on a screw. The two cranks were manipulated so as to keep the beam freely suspended. When the tension is increased sufficiently, the sample breaks, allowing the beam to drop to rest. The scale reading is, strictly speaking, the yield strength, but for practical purposes it may be considered to be the tensile strength.

The samples were fastened at each end by steel clamps, which were tightened with screws. Considerable pressure was required to prevent slipping, and it was soon found that unless the steel jaws were covered with some softer material the catgut was pinched sufficiently to impair its strength seriously. Covering the jaws with cardboard increased the readings of the yield strength on the samples of a particular strand of no. 1 plain catgut from an average of 3.94 to 6.59 Kg. After trial of several substances, white rubber tubing, such as is often used to prevent stay sutures from cutting the skin, proved to be the most satisfactory

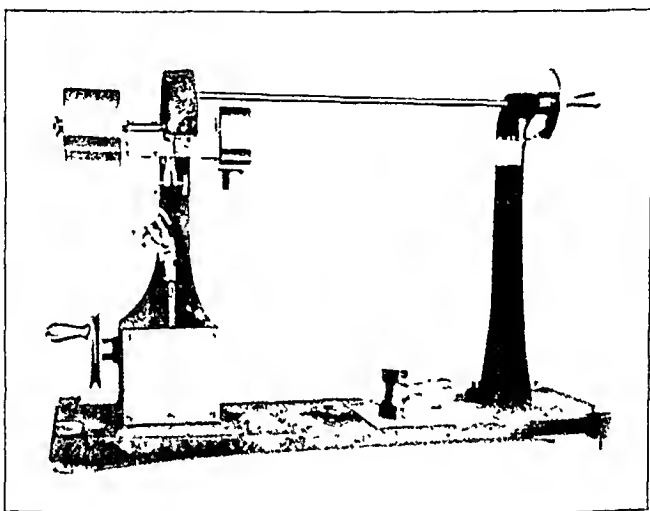


Fig. 1.—Apparatus for determining the tensile strength of catgut.

means of protecting the samples from the pinch of the clamps. A short section of the tubing was slipped over each end of the sample when it was clamped.

Commercial testing machines, such as are used for testing the strength of twine, etc., avoid inaccuracies due to the pinch of the clamps by taking a turn of the specimen about a 2 inch (5 cm.) cylinder before it is clamped. Special holders utilizing this principle were made for our apparatus. The cylinders were $\frac{1}{2}$ inch (1.3 cm.) in diameter. Catgut which broke at an average of 5.93 Kg. when clamped with rubber tubing broke at an average of 5.69 Kg. when clamped with the special holders. These results are essentially the same in view of the wide variations that run through all catgut. As the special holders required inconveniently long specimens, the rubber tube method was used for all subsequent experiments.

The length of the specimens, which were tested without knots, was usually about from 3 to 4 cm. As tensile strength is affected to some extent by moisture, specimens removed from tissues were allowed to dry before being tested.

Variations between consecutive samples from a single strand of catgut were surprisingly large. While occasionally a strand of catgut

would be weaker throughout than others of the same size, type and brand, in general the variations between samples from different strands of the same kind of catgut were of the same order of magnitude as the variations between different samples of the same strand. The variations actually found in a few strands are shown in table 3. From four to thirteen samples from each strand were tested. The difference between the average strength of samples of corresponding products of the three manufacturers whose catgut was tested were in general less than that found between individual samples from any one strand. Considerable variation has been found before in tensile strength tests on catgut. This is evidenced by the fact that Minervini made six determinations and averaged the results to get each of his figures. Bullock, Lampitt and Bushill (1929) found it necessary to average twelve determinations for their work on physical and chemical factors

TABLE 3.—*Variability of the Strength of Catgut in a Given Strand (Manufacturer A)*

Kind of Catgut	Minimum Tensile Strength, Kg.	Maximum Tensile Strength, Kg.	Average Tensile Strength, Kg.
Plain no. 0.....	4.86	8.04	5.93
Plain no. 0.....	5.63	8.44	6.57
Plain no. 0.....	4.00	6.15	5.11
Chromic no. 0.....	3.37	5.12	4.16
Chromic no. 0.....	5.13	5.48	5.41
Iodized tanned no. 0.....	2.47	3.35	3.02
Iodized tanned no. 0.....	3.42	5.98	4.31

in the manufacture of catgut. The difference in strength between no. 0 and no. 1 catgut was about 23 per cent.

Significant differences in the initial strength were found between catgut of different types, that is, between plain, medium-hard chromic and tanned iodized catgut. The plain catgut was the strongest, and the tanned iodized catgut the weakest. The medium-hard chromic catgut of manufacturer A is advertised as ten to twenty day chromic catgut and that of the other two manufacturers, as twenty day chromic catgut. Tanned iodized catgut is iodized in addition to being chromicized.

The mean initial strengths of the varieties used are shown in table 4. Beside each figure are shown the number of samples tested and the number of tubes from which they came.

Experiments on Dogs.—In the work on dogs the wall of the abdomen was used as the site for implantation in all cases. In all the experiments on which the results are based the ends of the suture were left outside of the body so that the suture could be removed without incision. This method is applicable to patients,

and it permits different samples of the same piece of catgut to be withdrawn on successive days and tested. It is, however, open to the following criticisms:

1. As shown by Ilyin (1908) the skin affects catgut much more rapidly than muscle, fascia or the subcutaneous tissues.

2. As shown by Bruns (1875) and by others, the absorption of catgut is greatly accelerated by infection. There is a tendency for skin sutures to give rise to stitch abscesses, particularly when left for over a week.

3. The part played by subclinical infection, that is, by infection without supuration, is not known. The deeper layers of the skin have been shown to harbor bacteria, even after careful disinfection of the surface. That such infection might accelerate absorption is conceivable. The hypothesis would furnish a facile explanation for Ilyin's observation. In experiments on patients absorption of catgut was more rapid in the wounds of inguinal herniorrhaphy, in which the roots of the pubic

TABLE 4.—*Mean Tensile Strength of Unused Catgut (Kilograms)*

Kind of Catgut	Manufacturer A	Manufacturer B	Manufacturer C
Plain no. 0.....	5.57 (24 samples, 10 tubes)	3.50 (9 samples, 9 tubes)	
Plain no. 1.....	6.83 (6 samples, 5 tubes)	5.22 (5 samples, 4 tubes)	
Chromic no. 0.....	4.66 (23 samples, 14 tubes)	4.88 (9 samples, 9 tubes)	5.50 (10 samples, 6 tubes)
Chromic no. 1.....	4.73 (8 samples,* 5 tubes)	5.84 (5 samples, 4 tubes)	
Tanned iodized no. 0.....	3.81 (20 samples, 8 tubes)	3.78 (1 sample, 1 tube)	5.16 (4 samples, 4 tubes)
Tanned iodized no. 1.....	4.97 (11 samples, 7 tubes)	4.57 (5 samples, 4 tubes)	

* One sample broke at 1.65 and was probably defective.

hair interfere somewhat with disinfection of the skin, than in other abdominal wounds.

The first criticism was met in our experiments by inserting a long enough section of the suture material into the deeper tissues, so that the portions in the skin could be avoided when the tensile strength was tested. The sutures were introduced on a long straight cutting edge needle, the point of which was forced through the skin and subcutaneous tissues and felt to pierce the fascia of the anterior rectus muscle before being brought out again. To prevent infection, careful asepsis was observed. The skin was prepared by shaving or close clipping and scrubbing with tincture of soft soap. It was then wiped off and painted with 7 per cent tincture of iodine and finally washed with 80 per cent alcohol.

The sutures were tied loosely so that they would not cut the skin, and an ample dressing was applied and protected with a strong binder.

Female dogs were selected whenever possible, and it was found essential to use animals with healthy coats.

When infections of the wound or stitch abscess occurred, the data were discarded. This invalidated several of the experiments on dogs but only a few of those on patients.

The influence of subclinical infection from the skin was tested to some extent by burying sutures completely and comparing their strength on removal with that of similar specimens inserted as skin sutures. The results were substantially the same. This, of course, does not exclude the possibility of such infection being present, but it does reduce the rôle it plays to the same rôle it might play in any wound which heals per primam intentionem. For this reason we feel that results by this method should have a more practical significance in relation to rupture of the wound than they would have had some more protected region of the body, such as one of the intraperitoneal organs, been used as the site for implantation.

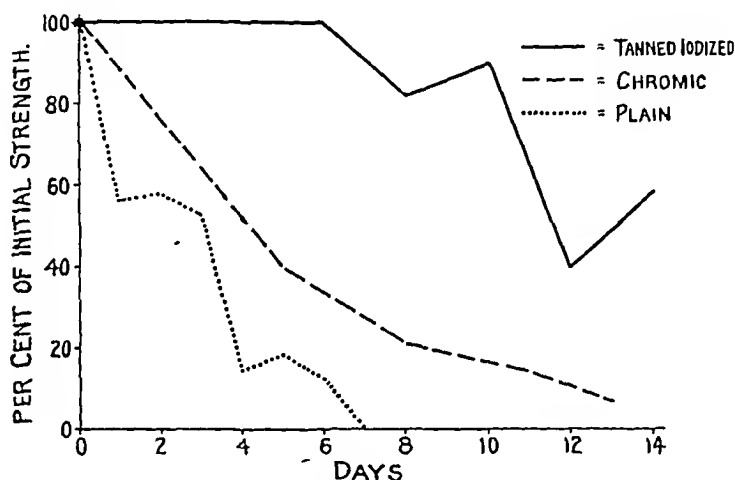


Fig. 2.—Graphs showing the strengths of samples of a single strand of catgut after the periods of implantation were increased in the same animal.

The results of the experiments on dogs have been expressed for the principal types of catgut tested in terms of the average daily decline in strength expressed as percentage of initial strength. This figure is computed as follows:

$$\frac{(\text{Initial Strength}) - (\text{Strength of the Last Specimen Tested})}{(\text{Initial Strength}) \times (\text{Number of Days the Final Specimen Remained Implanted})} \times 100$$

The results are shown in table 5.

Specimen graphs of individual experiments are shown in figure 2, each line representing the fate of one strand of catgut in a single dog.

Wide variations are again evident, but the data indicate a considerable difference between the three types of catgut. The chromic catgut retained its strength considerably longer than the plain catgut, as would be expected, but it was exceeded in durability still more by the tanned iodized variety. This was an unexpected finding.

Infection.—None of the experiments were directed toward studying the influence of infection, but in several of those instances in which

infection occurred, a rapid weakening of the suture material took place, as shown in table 6. This is in accord with many references in the literature to the fact that absorption of catgut is hastened by infection.

It was interesting to observe, however, that the effect was not pronounced with tanned iodized catgut.

While one does not anticipate infection in a clean abdominal wound, yet as infection does occur from time to time, this property of the tanned iodized suture may prove to be of tangible value.

TABLE 5.—*Average Daily Decline in Strength of Catgut of Manufacturers A and B in the Rectus Abdominis Muscles of Dogs*

Plain Catgut	Chromic Catgut	Tanned Iodized Catgut
14.1%	7.4%	2.8%

TABLE 6.—*Relation of Infection to Change in Tensile Strength After Contact with Body Fluids*

Manufacturer	Kind of Catgut	One Hour, Kg.	120 Hours, Kg.	Comment
A	Chromic no. 0	5.85	1.80 1.88 2.24	Not infected
A	Chromic no. 0	5.55	0.17 0.15 0.21 1.09	Infected
O	Chromic no. 0	5.54	2.34 1.95	Not infected
O	Chromic no. 0	5.07	1.35 0.24	Infected
A	Iodized tanned no. 1	4.04	3.37 3.69	Not infected
A	Iodized tanned no. 1	4.88	3.15	Infected
A	Iodized plain no. 1	6.51	3.26 2.97	Infected
B	Iodized tanned no. 0	3.78	2.09 2.34	Infected

Experiments on Patients.—The skin closure of a number of abdominal wounds was effected with catgut. The sutures were removed at various intervals of from one to twelve days and tested. All of the catgut used in this way was manufactured by Johnson and Johnson and was obtained from the regular stock of the general operating room. It was introduced as long vertical mattress sutures, so that about 3 cm. of catgut lay in the subcutaneous tissues. None of the wounds were drained except those in cases of operation on the gallbladder, and this was done as a safeguard against possible extravasation of bile or blood and not on account of infection. Mayer (1878) showed that human bile had little effect on catgut.

The data obtained are recorded in the graphs (figs. 3 to 8). When preliminary determinations of the initial strength were not made from a specimen of the catgut used, the average of all the other specimens of the same size and type of

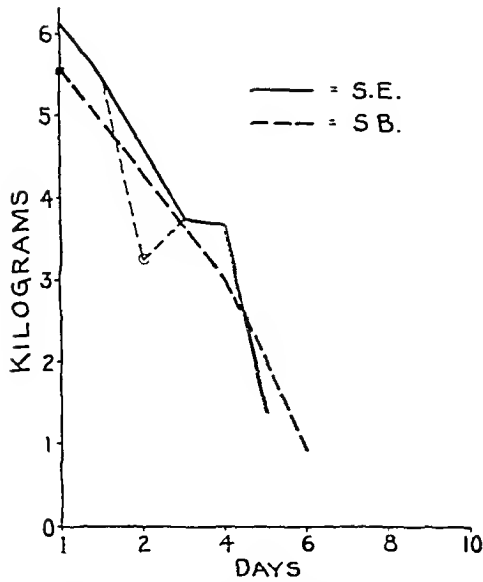


Fig. 3.—Graphs showing the decline in tensile strength of no. 0 plain catgut in patients S. E. and S. B.

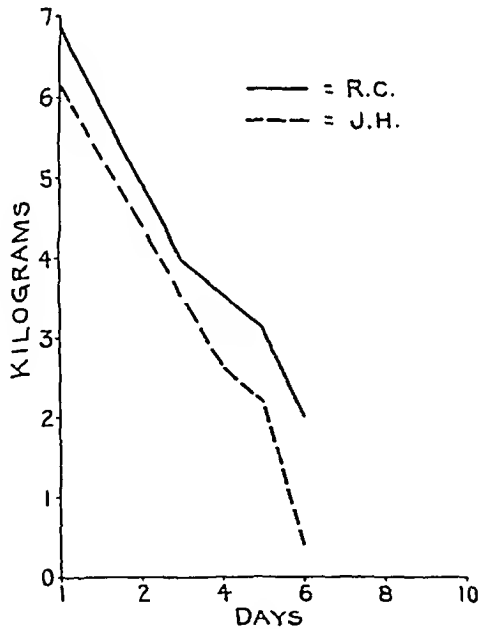


Fig. 4.—Graphs showing the decline in tensile strength of no. 1 plain catgut in patients R. C. and J. H. Infection of the wound developed in R. C. on the ninth postoperative day, and a small stitch abscess developed in J. H.

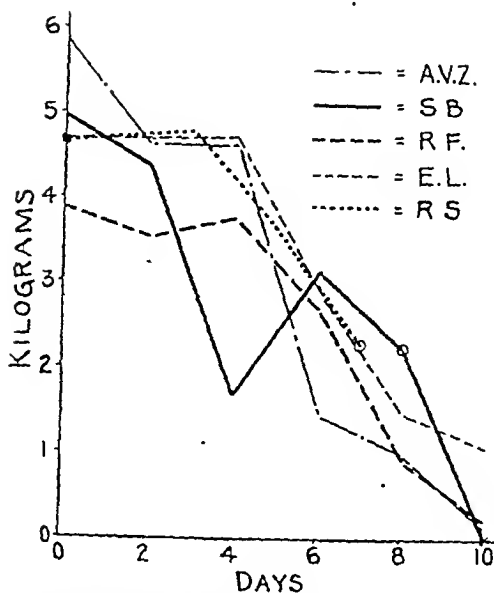


Fig. 5—Graphs showing the decline in tensile strength of no. 0 chromic catgut (ten to twenty day) in patients A. V. Z., S. B., R. F., E. L. and R. S.

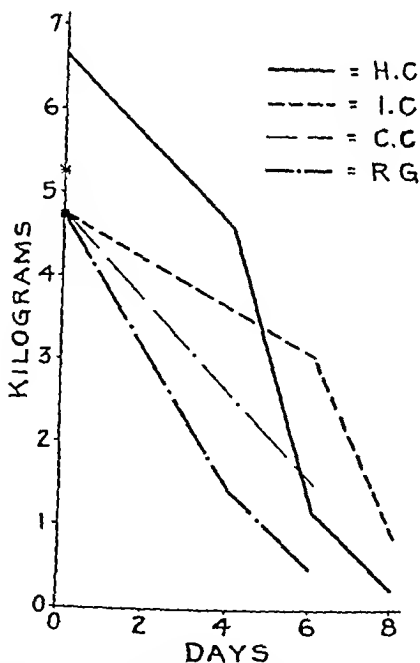


Fig. 6.—Graphs showing the decline in tensile strength of no. 1 chromic catgut (ten to twenty days) in patients H. C., I. C., C. C and R. G.

catgut which were tested was used. Such averages are designated on the graphs by squares instead of dots. Points indicated by circles may be subject to some inaccuracy, as when specimens were too short to fit the testing apparatus readily.

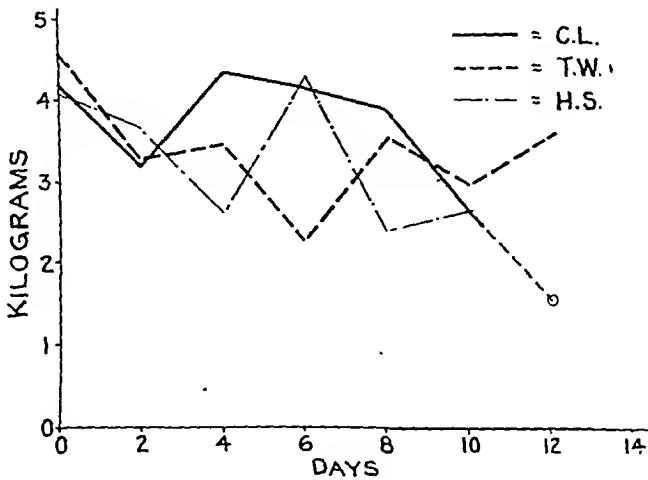


Fig. 7.—Graphs showing the decline in tensile strength of no. 0 tanned iodized catgut in patients C. L., T. W. and H. S.

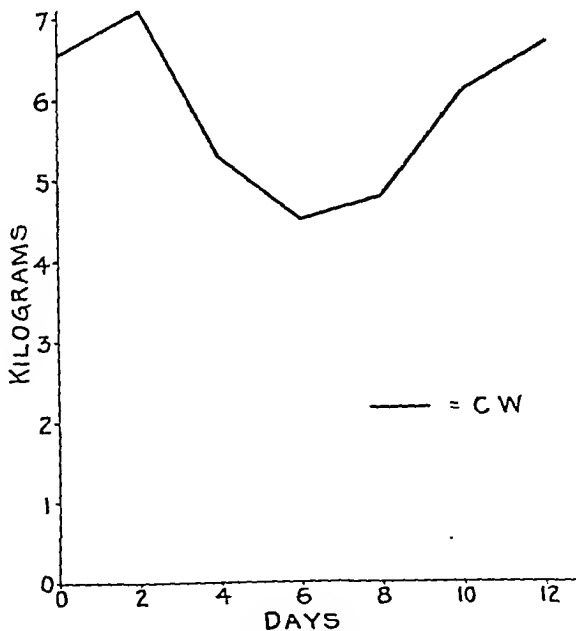


Fig. 8.—Graphs showing the decline in tensile strength of no. 1 tanned iodized catgut in patient C. W.

Infection occurred in two cases. In the first case a small purulent collection appeared a few days after all the specimens were removed, and in the second case a small bead of pus was present in the tract of one of the sutures. These two experiments were omitted from the averages shown in table 7.

From these data it appears that exposed to the subcutaneous tissues of man under actual operating conditions, Johnson and Johnson tanned iodized catgut has an average daily decline in tensile strength of less than half that of the medium hard chromic catgut of the same manufacturer and that the latter declines about two-thirds as rapidly as the plain variety.

As shown by the reports of cases collected by Sokolov (1931), rupture of the wound almost always occurs between the fourth and twelfth postoperative day. In most of the instances considered here it occurred by the eighth day, but in one it was delayed to the twelfth day. This agrees with the experimental work of Howes, Sooy and Harvey (1929) on the rate at which the tensile strength of a wound increases. Strength does not reach a maximum until on or about the twelfth day. Therefore, in closing fascia in an abdominal wound with catgut, particularly if excessive strain is anticipated, as from

TABLE 7.—*Average Daily Decline in Tensile Strength of Johnson and Johnson Catgut in the Subcutaneous Tissues of Patients*

Kind of Catgut	Percentage
Plain.....	14.8
Chromic.....	10.9
Tanned iodized.....	3.5

coughing or distention, we believe that tanned iodized catgut is the safest variety to use.

SUMMARY

The medical literature on the absorption of catgut is reviewed.

Tensile strength tests on fourteen kinds of catgut were made to show the variations: (a) between consecutive samples from the same strand of catgut; (b) between different strands of catgut of the same size, type and brand; (c) between sizes 0 and 1 of catgut otherwise identical; (d) between corresponding products of three different manufacturers, and (e) between plain, medium hard chromic and tanned iodized catgut of the same size and from the same manufacturer.

The decline in tensile strength of several kinds of catgut was tested by implantation of samples in the abdominal walls of dogs. This showed that tanned iodized catgut possessed substantially more resistance to the action of tissue fluids than medium hard chromic catgut.

Evidence was obtained which showed that tanned iodized catgut was much less affected by infection than medium-hard chromic or plain catgut.

About one hundred specimens of Johnson and Johnson catgut were implanted as skin sutures in abdominal wounds of patients. These

were withdrawn at intervals of from one to twelve days, and graphs were made of the results. The data showed also that tanned iodized catgut loses its strength much more slowly than medium-hard chromic catgut.

The decline in strength of catgut in man is approximately the same as in the dog.

As the methods of manufacturers of catgut are little publicized and of course subject to change without notice, the investigation of any particular brand of catgut may be of rather temporary significance. It is, however, a fairly simple matter to test catgut for its lasting power either at regular intervals or whenever suspicion of change arises. We are convinced that man is the most suitable subject for these experiments as well as being the most easily available to the practicing surgeon.

Dr. I. S. Ravdin gave suggestions and criticisms in connection with this work.

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INFLUENZAL MENINGITIS

REPORT OF A CASE WITH RECOVERY

ISIDORE COHN, M.D.

NEW ORLEANS

Individual case reports should be made if there are sufficient grounds for believing that something unusual is to be presented. In the instance under consideration there are many instructive, puzzling and gratifying experiences which form the basis for inquiry and for a statement of the record.

Deductions of dogmatic character cannot be drawn, but it is safe to add these experiences to those already accumulated, and from the whole some inference may be justifiable.

In order to bring the problem at once before the reader, a summary of the salient facts will be given here and elaborated on later in the paper.

REPORT OF CASE

S. S., a child aged 11 years, was injured in an automobile accident on March 23, 1935. He was picked up by a passing motorist and taken to an institution, where roentgenograms of the skull and one of the clavicle were taken. The original pictures were interpreted as "negative for bone injury." After receiving this report I had the child immediately transferred to the Touro Infirmary, where roentgenograms were again taken of the clavicle and the skull.

From the roentgenologic department the child was taken to the operating room. He was alert and excitedly conscious. The skin was extremely pale, cold and clammy. The pupils were equal and reacted to light and in accommodation. The only evident deformity was that of the left clavicle, which showed a definite angulation and a fulness in the left supraclavicular region; the shoulder on that side was on a lower level than that on the right. A bleeding wound behind the left ear was noted. In order to determine the nature of this wound ethylene was administered. When the flap of skin behind the ear was elevated, a tongue of lacerated brain tissue was seen protruding through an opening in the skull, which could easily have admitted the tip of the little finger. There was a free discharge of cerebrospinal fluid. Above the ear there was a definite depression. A prophylactic dose of mixed gas gangrene and tetanus serum was given.

He was returned to the room; an infusion of a 5 per cent solution of dextrose was given, and 3 ounces (88.7 cc.) of magnesium sulfate was ordered given by rectum every eight hours. Heat was applied to the extremities and an ice bag to the skull.

An oculist, Dr. Hardin, examined the eyegrounds immediately and at frequent intervals during the patient's stay in the hospital. At no time did he find evidence suggestive of increase of intracranial tension.

From the Department of Surgery, Graduate School of Medicine, Tulane University, and Touro Infirmary.

After receiving 500 cc. of the dextrose infusion the patient had a severe chill and became irrational and extremely restless. The restlessness persisted for hours, as did the incoherent talking. Vomiting, which began two hours after admission, persisted.

Readings of blood pressure were made at frequent intervals. The variations were slight, the pressure remaining between 115 systolic and 75 diastolic and 108 systolic and 70 diastolic.

The patient's color remained good; the volume of pulse was good, the rate was 90 and the rhythm was regular.

On March 28, five days after the accident, the child had a chill and a rise of temperature to 102.4 F. The wound was inspected and found to be granulating. There was no evidence of local infection, and the regional lymph nodes were not enlarged. There was a marked rise in the pulse rate.

Two conditions were thought of, one the possibility of an infection of the upper respiratory tract and the other a delayed serum reaction. The blood count at that time showed a white cell count of 5,650, with 8 per cent eosinophils. Because of the leukopenia, the general condition of the wound, the absence of swelling in the left side of the neck in the region of the jugular vein and the absence of regional glandular enlargement, I did not feel that the fever was due to an intracerebral condition or thrombosis of the lateral sinus. He complained of a general itching of the body, and this, coupled with the fever, suggested a delayed serum reaction.

The following day edema of the face, generalized urticaria, itching and vomiting, with persistence of fever, left no doubt that I was dealing with a serum reaction. The febrile reaction persisted for two days, after which the convalescence was so uneventful that it was hard to believe that a patient who had been so seriously injured was improving so consistently.

The child was kept in the hospital until April 13, when he was allowed to go home in the ambulance; there he was kept quiet and under a strict regimen to avoid anything which might give rise either to an infection or to an increase in the intracranial tension, the possibility of abscess of the brain or meningitis as sequelae being kept in mind.

All went well at home until April 24, when the child complained of a headache and a sore throat. Dr. Taquino, an otolaryngologist, noted a redness of the throat, which he thought might possibly account for the fever.

The following morning a blood count was made by Dr. Foster Johns. The leukocyte count was 23,500, with 95 per cent neutrophils. Examination of the urine showed a trace of albumin, sugar and numerous hyaline casts.

The child was immediately taken to the Touro Infirmary. On examination it was noted that the pupils were equal, reacted to light and in accommodation and revealed no evidence of an oculomotor disturbance. The eyegrounds were normal. Dr. Taquino reported that the ear drum was red, but it did not bulge. The eyes were examined, and no evidence of pressure was noted.

A roentgenogram of the skull was taken, and this showed cloudiness in the region of the left mastoid and the old depressed fracture.

Because of the headache, vomiting and febrile reaction, the presence of sugar in the urine and the marked leukocytosis, it was decided to do a spinal tap to determine the presence of meningitis.

Ethylene anesthesia was used. The spinal fluid obtained was cloudy. A mercury manometer registered a pressure of 40 mm. The pressure was reduced to less than 12 mm. by drainage. While the child was under the influence of the anesthetic, paracentesis of the left ear was done and thick pus was evacuated

TABLE 1.—*Résumé of Findings on Spinal Punctures*

Date	Pressure Before Tap, Mm. of Hg	Pressure Reduced to Mm. of Hg	Quantity of Fluids Removed, Cc.	Color of Fluid	Cell Count	Globulin	Differential Cell Count	Culture
4/25/35	40	12	..	Cloudy	10,800	4 plus	78 per cent neutrophils; 22 per cent lymphocytes	Gram-negative bacilli, morphologically B. influenzae
4/26/35	26	10	..	Less cloudy	11,400	3 plus	Few lymphocytes; many pus cells	Gram-negative bacilli, morphologically and culturally B. influenzae
4/27/35	50	..	90	Cloudy	6,400	2 plus	Gram-negative bacilli, morphologically and culturally B. influenzae
4/28/35	30	12	45	Cloudy	1,150	1 plus	Gram-negative bacilli, morphologically and culturally B. influenzae
4/29/35	50	12	..	Flakes	320	1 plus	Morphologically and culturally B. influenzae
4/30/35	22	10	45	Clear	525	1 plus
5/ 1/35	60	12	60	Cloudy	600	1 plus
5/ 2/35	90	8	60	Cloudy	1,075	1 plus
5/ 3/35	80	10	45	Not so cloudy	1,110	1 plus	Pellicle formation; smear contained all polymorphonuclear cells; no organisms
5/ 4/35	62	4	45	Much clearer	625	1 plus
5/ 5/35	56	4	..	Much clearer	825	1 plus
5/ 6/35	66	6	50	Flakes	1,170	Negative	100 per cent polymorphonuclears; no organisms	B. influenzae
5/ 7/35	60	10	2,550	2 plus	B. influenzae
5/ 8/35	66	8	50	1,460	1 plus	80 per cent neutrophils	B. influenzae
5/ 9/35	66	8	98	Much clearer	725	1 plus	B. influenzae
5/10/35	66	6	..	Clear	850	1 plus	No growth
5/11/35	44	8	30	Clear, few flakes	375	1 plus	No growth
5/12/35	44	8	15	Clear	505	Negative	No growth
5/13/35	42	8	30	Yellowish tinge	325 (polymorphonuclears in red blood cells)	1 plus	No growth
5/14/35	42	8	20	Xanthochromia	78 (polymorphonuclears)	1 plus	No growth
5/15/35	34	8	50	Clear	85 (polymorphonuclears)	1 plus	No growth
5/17/35	40	8	40	Clear	162	60 per cent lymphocytes, 40 per cent polymorphonuclears	No growth

TABLE 1.—*Résumé of Findings on Spinal Punctures—Continued*

Date	Pres- sure Before Tap, Mm. of Hg	Pres- sure Re- duced to Mm. of Hg	Quan- tity of Fluids Re- moved, Cc.	Color of Fluid	Cell Count	Globulin	Differential Cell Count	Culture
5/19/35	38	10	40	Clear	105 (few poly- morpho- nuclears)	Slight trace	No growth
5/20/35	40	8	50	Clear, flakeless	...	Nega- tive	35 per cent lymphocytes
5/23/35	28	10	25	Clear, few flakes	...	Slight trace	70 lympho- cytes; 5 per cent poly- morpho- nuclears	Gram-positive cocci, Staphylo- coccus aureus
5/26/35	26	8	20	Clear	52	Slight trace	Negative
5/31/35	12	..	1	Clear, no flakes	26 lympho- cytes	No growth

When the child awakened, he was mentally clear and there was less headache. An organism morphologically and culturally *Bacillus influenzae* was noted in the spinal fluid. The white cell count was 10,800.

The following morning, April 26, the child complained of a headache and of pain and stiffness of his neck. The reflexes in the extremities were not exaggerated. The temperature rose to 104 F. The pulse rate ranged between 120 and 140. The pupils remained equal.

A second spinal tap was done at 1 p. m. The pressure was found to be 26 mm. The fluid was cloudy but less so than the day before.

On April 27 the temperature reached a maximum of 104.6 F. Neither vomiting nor drowsiness was noted.

The daily spinal tap revealed a pressure of 50 mm., but the fluid seemed less cloudy. About 90 cc. of spinal fluid was withdrawn before the pressure was reduced to 12 mm.

After the tap the patient ate well. He complained of headache only during the afternoon. He slept the greater part of the night quietly and without drugs.

On April 28 the child seemed alert, felt well, with no headache, nausea or vomiting and was interested. Spinal tap was performed; the maximum pressure was 20 mm. The fluid was distinctly less cloudy than on previous occasions; the pressure was reduced to 12 mm. by the removal of 45 cc. The blood pressure was 128 systolic and 85 diastolic.

On April 29 spinal tap was performed; the pressure was from 46 to 50 mm. and was reduced to 12 mm. The blood pressure was 118 systolic and 85 diastolic.

On April 30 spinal tap was performed; the pressure was 22 mm. It was reduced to 11 mm. when 45 cc. of fluid was drained.

On May 1 spinal tap was performed; the pressure was 60 mm. and was reduced to 12 mm. The fluid was slightly cloudy. A transfusion of 200 cc. of whole blood was made.

On May 2 headache was complained of. The pressure of the spinal fluid was found to be 90 mm. It was reduced to 10 mm. when 60 cc. of fluid was withdrawn.

On May 3 spinal tap was performed with the patient under general anesthesia. The pressure was 80 mm.; 45 cc. of fluid was removed, and the pressure was reduced to 10 mm. The fluid was much clearer.

On May 4 spinal tap was performed. The pressure was 62 mm. About 50 cc. of fluid was withdrawn, and the pressure was reduced to 4 mm. The fluid was clear.

On May 5 spinal tap was performed; the pressure was 56 mm. The fluid seemed clearer than on May 4. Blood was taken for a count.

After puncture the patient rested well, not complaining of headache, and was mentally more alert. The pulse was of good volume; the rate was 100. He took nourishment freely. The temperature was 102.2 F.

On May 6 spinal tap was performed at 8:15 a. m. The pressure was 66 mm. Flakes were present. About 50 cc. of fluid was withdrawn and the pressure was reduced to 6 mm.

Eight hours after the tap the patient complained of pain in the back of the head. The pain did not seem to be more severe than that felt at the same time on May 6. The blood pressure was 102 systolic and 72 diastolic. No change was noticeable in the volume of the pulse. The patient was mentally clear.

TABLE 2.—Results of Examination of Blood

Date	Red Cells	White Cells	Hemo- globin Content, %	Seg- mented Cells, %	Staff Cells, %	Smear				
						Young Forms, %	Poly- morpho- nuclears, %	Lym- pho- cytes, %	Mono- cytes, %	Eosino- phils, %
3/24/35	4,070,000	11,450	..	74	7	0	..	16	2	1
3/28/35	5,200,000	5,650	72	19	1	8
3/30/35	7,850	37	53	1	4
4/26/35*	4,570,000	18,500	78	52	42	3	..	6
4/28/35	4,320,000	10,750	75	40	25	5	..	28	2	..
5/ 1/35	4,575,000	27,750	75	85	14	1	..
5/ 5/35	4,715,000	22,500	75 to 80	78	19	3	..
5/ 9/35	4,625,000	14,500	75	84	40	3	..
5/19/35	4,710,000	9,500	80	57	40	8	..

* On April 26 the sugar content of the blood was found to be 100 mg. per hundred cubic centimeters.

On May 8 spinal tap was performed; the pressure was 66 mm. About 56 cc. of fluid was withdrawn, and the pressure was lowered to 8 mm. A transfusion of 250 cc. of whole blood was given.

On May 9 spinal tap was performed in the morning; the pressure was 66 mm. About 98 cc. of fluid was withdrawn, and the pressure was reduced to 8 mm. The fluid seemed to be much clearer than it was on May 8. At 10:30 a. m. the patient was awake and ate breakfast. He said that the headache was better. He was mentally very clear and observant. The pulse showed good volume.

On May 10 spinal tap was performed; the pressure was 66 mm. and was reduced to 6 mm. The fluid was clear. Two hours later he was awake and not complaining of headache.

On May 11 spinal tap was performed; the pressure was 44 mm. The fluid was clear, with few flakes. About 30 cc. was withdrawn, and the pressure was reduced to 8 mm.

On May 12 spinal tap was performed; the pressure was 44 mm. and was reduced to 8 mm. About 15 cc. of fluid was removed. The fluid was much clearer than it had been at any time; few flakes were present.

On May 13 spinal tap was performed; the pressure was 42 mm. and was reduced to 8 mm. The fluid had a yellowish tinge. Although the pressure was

less than it had been on May 12, the total amount of fluid withdrawn was greater—about 30 cc. Five hours later the patient was talking, very responsive and not complaining of headache.

On May 14 spinal tap was performed; the pressure was 42 mm. About 20 cc. of fluid was removed. The yellow tinge was still present. The patient was sleeping. Examination of the eyes showed no abnormality.

On May 15 spinal tap was performed; the pressure was 34 mm. and was reduced to 8 mm. by removal of about 50 cc. of fluid. The fluid was clear, showing only a slight trace of xanthochromia, if any.

On May 16 the patient appeared alert and did not complain of any pain.

On May 17 spinal tap was performed for the first time since May 15. For several hours the child had no headache. The spinal fluid pressure was 40 mm. and was reduced to 8 mm., about 40 cc. of fluid being withdrawn. The fluid was clear, with few flakes.

On May 19 spinal tap was performed; the pressure was 38 mm. and was reduced to 10 mm. About 40 cc. of fluid was removed. It was clear, with few flakes. Notes made that evening reported that the patient was alert and very talkative, making no complaint of pain. The blood pressure was 112 systolic and 88 diastolic.

On May 20 spinal tap was performed; the pressure was 40 mm. and was reduced to 8 mm., about 50 cc. of clear, almost flakeless fluid being withdrawn.

On May 21 the patient did not complain of any discomfort and was alert and responsive to all questions.

On May 22 the patient had a comfortable day. He did not complain of headache. He was very alert and did not want another spinal puncture done.

On May 23 spinal tap was performed at 8:30 a. m.; the pressure was 28 mm. and was reduced to 10 mm., about 25 cc. of fluid being withdrawn. The fluid was clear, with very few flakes. Eight hours after the spinal tap the child was talkative, alert and much interested.

On May 25 the patient was talkative and alert and had no headache.

On May 26 spinal tap was performed; the pressure was 26 mm. and was reduced to 8 mm., about 20 cc. of clear fluid being removed.

On May 27 the patient was talkative and had had no headache for over a week.

The last spinal tap was performed on June 2, the pressure being 12 mm. The fluid was clear, with no flakes. One cubic centimeter was removed for a cell count.

On June 4 the report showed that the patient had been alert and uncomplaining so far as headache was concerned. The bowels had acted freely. The urine was free from reducing action. No disturbance of vision was apparent. The general appearance was excellent. He had been in the courtyard for the past several days.

On June 11 examination of the eyes showed no abnormality. The eyegrounds were normal. Daily examinations were made by the oculist, and at no time did he observe changes of the retina.

COMMENT

Looking back over this case, I find that the interpretation of the original roentgen plates failed to give the information that the depressed fracture of the skull existed. Even a repetition of the roentgen examination after the clinical examination had definitely shown the existence of the compound fracture with laceration of the brain failed to demon-

strate satisfactorily the abnormal opening in the skull. This may be accounted for by the fact that a Bucky diaphragm was not used. Whatever the reason, this is evidence that the laboratory diagnosis should not be used to the exclusion of a clinical examination. This is an additional proof of the necessity for making a careful examination in order that one may not be misled by diagnostic aids. The day of the clinician is not over. Careful examination, the utilization of all clinical data and the exercise of judgment acquired by years of experience are not to be replaced by the exclusive reliance on laboratory data.

The mortality from head injuries has been materially diminished, as statistics show, by the use of conservative, nonoperative measures. The treatment instituted in this case consisted of dehydration and limited intake of fluid. Magnesium sulfate was given by rectum instead of by the oral route, because it is desirable to avoid anything which will even temporarily raise the intracranial pressure. Vomiting raises the intracranial pressure. Magnesium sulfate administered by mouth at times produces this unwanted symptom.

At the time of the accident there was no indication for spinal drainage, as there was a persistent cerebrospinal decompression through the dural wound. Fortunately there did not develop an infection at the site of the wound; in fact, the wound granulated rapidly and healed like a wound of the mastoid.

At no time did the eyegrounds show any abnormal changes. This I took to be a good sign, indicative that the intracranial pressure was not increased. That this was not a justifiable conclusion the subsequent course proved.

With the sole exception of the serum reaction, the convalescence of the patient from the fracture and laceration of the brain was uneventful; his wound granulated well, and no manifestations of intracranial pressure developed.

When the prospects seemed to be better, the family were anxious for a favorable prognosis. Late manifestations of abscess of the brain or meningitis were kept in mind, and a guarded prognosis was given. Continually the attitude was assumed that each day represented so much gained.

As stated before, on April 13, twenty-one days after the accident, the patient was taken home. Still the caution was observed of keeping him quiet, undisturbed by company.

All went well for two weeks, when the child complained of headache, and the nurse noted a temperature of 101 F. As noted in the record, he was examined by Dr. Taquino, who found evidence of a red throat, which suggested that the fever might be due to an intercurrent infection of the respiratory tract. However, evidence of marked leuko-

cytosis, there being 23,500 white blood cells, with 90 per cent neutrophils, an increased pulse rate and urinary findings of sugar, albumin and casts, added to the symptoms of headache, nausea and vomiting, pointed to the need for immediate spinal puncture.

On his return to the hospital this was done, and the spinal fluid, which was under pressure of 40 mm. of mercury, was observed to be cloudy. After the spinal tap the middle ear was drained of thick purulent material by Dr. Taquino, the otolaryngologist.

It should be observed at this point that the diagnosis of meningitis might have been delayed if the ear had been punctured before the tap, because finding pus in the middle ear might have made one hesitant to do a spinal puncture. It might have been argued that the infection of the ear accounted for all the symptoms.

The report from the laboratory on the spinal fluid was anxiously awaited. The cell count was 10,800 and the reaction for globulin three plus, and a gram-negative bacillus, morphologically *B. influenzae*, was recovered from the culture.

Here, then, I was confronted by influenzal meningitis. What could be done and what was the prognosis? Little comfort could be obtained by reference to the literature and less from my colleagues.

A definite policy was adopted at once. It was decided to do daily spinal taps and repeated transfusions. In all, twenty-nine taps were done. The manometric readings during the first two weeks varied between 40 and 60 mm.; during the third, fourth and fifth weeks the pressure varied between 90 and 60 mm. Globulin, varying in quantity, was always present. The cell count varied between 11,400 and 52 during the convalescence. At one time the cells were all polymorphonuclear, and culturally an organism morphologically *B. influenzae* was observed during the first four weeks. The fluid varied from very cloudy to cloudy with flakes, and during the fifth week a definite xanthochromia developed. This persisted for a few days. The temperature ranged from 104.6 F. to 100 F. for four weeks; then the maximum temperature gradually declined to 100 F. and remained at that level with fluctuations down to 99 F. for another four weeks.

At no time during the illness was the child irrational; on the contrary, he was alert. When the pressure was high during the morning before the tap, he complained of a violent headache. Nausea and vomiting were not prominent manifestations.

A remarkable aspect of the case was the absence of disturbances of the eyegrounds; there was never any evidence of papilledema or retinal hemorrhage in spite of an intracranial pressure which reached a level of 90 mm. at one time. Neither did diplopia or other pressure phenomena develop.

It is hard to believe that an intracranial pressure of 90 mm. of mercury can exist without producing some signs in the eyes. It is the unusual, unexplainable manifestation which divests dogmatism of authority.

These facts demonstrate that evidence of increased intracranial pressure is not always obtainable by the expected changes in the eye-grounds. Dr. Hardin has informed me that in many cases of increased intracranial tension similar negative findings have been reported.

The policy of treatment consisted, in addition to the daily spinal taps, of repeated transfusions of whole blood, administration of magnesium sulfate by rectum for dehydration, a dry diet and the use of hypnotic drugs to overcome restlessness.

One may well imagine that the finding of meningitis culturally due to the influenza bacillus caused great concern. Turning to the literature, one finds many interesting clinical reports, compilations, experimental observations and deductions. In 1931 Bloom,¹ of New Orleans, reported a recovery after treatment by repeated spinal taps and replacement by convalescent serum. It is interesting to note that after twelve days of punctures and replacement with serum the culture was positive for four consecutive days in his case. Bloom reviewed the literature up to that time. He noted that the mortality was 92.5 per cent. In all the literature he was able to find reports of only twenty-four cases in which the patient had recovered.

In 1931 Jenks and Radbill² reported the cases of ten patients treated with influenza serum without a recovery.

In 1933 Wilkins³ reviewed the literature. The following is quoted from his article:

There are reports of only eight cases treated by serum—complement mixtures. In these cases the dose was 6-8 cc. of fresh human serum plus 15 cc. of influenzal antiserum. Treatment was given twice a day, alternating ventricular and lumbar injections with occasional cisternal injections. Ward states, "In the first five cases some improvement took place temporarily, although all of the five patients died eventually. In the next two cases, the disease was very far advanced on admission to the hospital, and not even temporary improvement was noted. . . ."

Since recoveries do occur spontaneously and have been reported in cases treated by lumbar puncture alone, by antimeningococcus serum, by influenzal vaccine, and by convalescent serum, great caution must be used in attributing any recovery to the therapeutic agent employed.

In 1934 Neal, Jackson and Appelbaum⁴ reviewed their own experiences in the treatment of one hundred and eleven patients, with four

1. Bloom, C. J.: *New Orleans M. & S. J.* **83**:455, 1931.

2. Jenks, H. H., and Radbill, S. X.: *Arch. Pediat.* **48**:1, 1931.

3. Wilkins, Lawson: *Internat. Clin.* **2**:300, 1933.

4. Neal, Josephine B.; Jackson, H. W., and Appelbaum, Emanuel: *Meningitis Due to the Influenza Bacillus of Pfeiffer (Hemophilus Influenzae)*, *J. A. M. A.* **102**:513 (Feb. 17) 1934.

recoveries. Their four instances of recovery brought the number up to thirty-five. The mortality, as cited by them, is 96.4 per cent.

They stated:

A study of the treatment of these thirty-five patients who recovered shows that twenty-six had lumbar punctures only or lumbar punctures supplemented by nonspecific therapeutic measures. The use of "convalescent serum" is mentioned in three instances. This, however, cannot be regarded as specific therapy, since the serum was obtained from individuals who had recovered from clinical influenza, which is not now considered to be caused by influenza bacilli. It seems obvious, therefore, that lumbar puncture is an important therapeutic measure. . . . Only eight patients received antiinfluenza serum. Of these, four patients were in our own group, and . . . in none of them could the use of the specific treatment be regarded as a determining factor in recovery.

Further research should be done toward the development of a more potent serum with high antitoxic as well as antibacterial properties.

One of the most important contributions to the subject was the work of Margaret Pittman,⁵ published in 1933. She stated that the organisms present in influenzal meningitis are "type specific" and "immunologically identical." This fact suggested to her as it did to other observers that a highly immune serum might have a specific therapeutic value.

Martha Wollstein, according to Neal, gave "the first real impetus to the study of influenza bacillus meningitis" (1911).

Wollstein did not find *Haemophilus influenzae* antiserum effective in treating children, although she found it effective in treating monkeys suffering from meningitis experimentally produced.

Pittman reported that eighteen patients have been treated by means of intrathecal injections of immune horse serum. She stated: "The results do not indicate that this form of specific therapy carried out under given directions was of great practical value."

It is at the present time accepted generally that influenzal meningitis is a primary disease. A great many of the observers have shown that an infection of the respiratory tract did not precede the onset of influenzal meningitis. Since there is not sufficient evidence to support the idea that such infection is a precursor of influenzal meningitis and since immunity from infection with influenza or grip is transient, the suggestion of using human serum from a patient who had influenza was not accepted in my case. Had I used it and had the patient recovered, I should have been inclined to attribute the happy result to the serum.

The results thus far obtained from influenza antiserum, or horse serum, given intraspinally are, to say the least, not impressive. When so large an area as the cerebrospinal system is involved, any agent to be effective must bathe the entire area in sufficient concentration to be able

5. Pittman, Margaret: J. Exper. Med. 58:683, 1933.

to combat effectively the living colonies present. It seems more logical at present to depend on drainage. Drainage favors natural irrigation. As long as the infection is present, the sources of serous fluids are stimulated to increased output. This has been demonstrated beautifully in the epoch-making work of Willems on joints.

The hyperactivity of the choroid plexus in the presence of infection is great. Free drainage is a surgical principle. All who have reported on the treatment of meningitis of influenzal character have advocated repeated spinal taps.

Repeated spinal taps were performed daily in this case, fluid being removed in variable quantities, and each time the tap was done an effort was made to reduce the pressure to slightly above the normal.

Several things were particularly noticeable about the results of the spinal drainage: 1. The quantity of fluid removed to reduce the pressure to a certain level was not constant. 2. The presence of flakes increased in proportion to the diminution of the cloudiness in the fluid. 3. As the cloudiness and the number of flakes diminished, the pressure became notably lower. 4. At one time the spinal fluid showed a definite xanthochromia. 5. The spinal fluid remained culturally positive for four weeks. 6. When the culture became negative, the temperature curve began to decline. These observations, with accumulated evidence from other cases, may prove to be of value.

Believing that the logical method of handling a patient with such a condition consisted of repeated taps and transfusions, I used these procedures as sheet anchors, and all other methods were avoided. No other procedures have been so consistently utilized in the reported cases in which the patient recovered. So far it seems that other procedures have been incidental to the individual patient's recovery.

SUMMARY

This case has been reported in detail for the following reasons:

1. A child who had a compound depressed fracture of the skull with brain laceration and a fracture of the clavicle recovered.

2. This patient five weeks after the accident acquired acute influenzal meningitis.

3. A persistent increased intracranial pressure, varying from 90 to 40 mm., was never associated with changes of the eyegrounds.

4. After 29 spinal taps and three transfusions I was fortunate enough to be able to report a complete recovery without evidence of any residual manifestations.

5. Up to the time of writing the efforts to prove the efficacy of so-called immune human serum have not been satisfactory.

6. It seems generally accepted that influenzal meningitis is a primary disease not associated with a previous infection of the respiratory tract in the majority of instances.

7. The organism causing influenzal meningitis is immunologically type specific.

8. The efforts thus far to effect cures with immune horse antiserum have failed in the human patients, although it has been effective in monkeys experimentally infected.

9. Until an effective antiserum is available, repeated spinal taps, transfusions, dehydration and sedatives remain the most valuable methods of attempting to aid influenzal meningitis.

10. The mortality remains about 96 per cent.

11. There is much work to be done before this dreaded disease is taken out of the column of almost certainly fatal diseases.

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INTRAMURAL FORMATION OF GALLSTONES

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Very little appears in the English medical literature concerning the formation of gallstones in the wall of the gallbladder. In fact, it has been impossible to find a single article which describes this condition fully.

Rolleston and McNee¹ briefly stated that intramural gallstones may occur, and in Sieveking's English translation of Rokitansky's "Manual of Pathological Anatomy," published in 1855,² a note is found regarding the occurrence of such stones.

Stones within the wall of the gallbladder were first described by Morgagni³ in 1761 in his famous "De sedibus et causis morborum." He thought that the stones originated in small glands. Outpouchings of the mucosa of the gallbladder into the external layers of its wall were first noted by Rokitansky in 1842,⁴ and in the English edition of the previously mentioned manual there occurs this sentence: "Small calculi are also occasionally formed within small saccular dilatations of the biliary mucous membranes and may appear to lie external to the cavity of the gallbladder." In the German edition of the same book, published in 1861,⁵ Rokitansky again stated that hernia-like diverticula of the mucous membranes are present in the gallbladder sometimes in great numbers, but that they are usually insignificant, with very small openings into the lumen, which explains why the dark-colored concretions often found in them appear to be placed between the layers of the wall of the gallbladder.

In 1858 Luschka⁶ published his first study on the glands of the human gallbladder. He may well have observed what will later be

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1. Rolleston, H., and McNee, J. W.: *Diseases of the Liver, Gall-Bladder and Bile-Ducts*, London, The Macmillan Company, 1929, p. 780.

2. Rokitansky, C.: *A Manual of Pathological Anatomy*, translated by E. Sieveking, Philadelphia, Blanchard & Lea, 1855, vol. 2, p. 130.

3. Morgagni, J. B.: *De sedibus et causis morborum*, translated by B. Alexander, London, Millar & Cadell, 1769, book 3, vol. 2, letter 37, article 21, p. 235.

4. Rokitansky, C.: *Handbuch der speziellen pathologischen Anatomie*, Wien, Braumüller and Seidel, 1842, vol. 2, p. 374.

5. Rokitansky, C.: *Lehrbuch der pathologischen Anatomie*, Wien, W. Braumüller, 1861, vol. 3, p. 282.

6. Luschka, H.: *Die Drüsen der Gallenblase des Menschen*. *Ztschr. f. rat. Med.* 4:189-192, 1858.

termed "Rokitansky-Aschoff sinuses," but he is given credit only for describing the so-called "true Luschka ducts." He studied gallbladders by rendering their mucous membrane transparent with acetic acid and then placing them on a glass slide in front of a bright light. By this means he found glands in the submucosa to be more numerous in the lower segment of the gallbladder. In some glands he found granular detritus and in others "bile-pigmented molecules." Cysts were also found in the submucosa, which he thought to be cystic degeneration



Fig. 1.—The photomicrograph showing a "true Luschka duct;" $\times 247$. These ducts lie on the undersurface of the liver, between it and the gallbladder; they are lined by tall columnar epithelium and fail to empty into the lumen of the gallbladder. Luschka regarded them as metamorphosed rests of the primordium of the liver.

of the glands following obstruction. In his "Anatomie des Menschen," published in 1863,⁷ he still maintained that the gallbladder has few glands but that they are never entirely absent. He then described what are called "true Luschka ducts," in which he was unable to find an opening into any space, and which he concluded were metamorphosed rests of the embryonal primordium of the liver (fig. 1).

7. Luschka, H Anatomie des Menschen, Tubingen, Lapp & Siebeck, 1863, vol. 2, p 256

Mueller,⁸ in 1895, wrote that he had never observed glands in the normal gallbladder but that he had found them in great numbers in all gallbladders with stones. In his opinion, the mucus secreted by the glands is necessary for the formation of stones.

Létienne⁹ in 1895 and Péraire¹⁰ in 1903 and others reported finding stones within the wall of the gallbladder, and much discussion ensued as to how they got there. Many observers attributed their presence to ulceration, as they found no epithelium about the stones, while others believed that they were formed in mucous glands which were then closed.

It remained for Aschoff¹¹ in 1905 to clear up the situation by means of a study of 145 gallbladders, of which number 6 were free from stones. In this study he divided the wall of the gallbladder into five layers: the mucosa, the muscularis, the fibrosa, the subserosa and the serosa, of which only three layers are now recognized by the "Basle Nomina Anatomica," i. e., the mucosa, the muscularis and the serosa.

Aschoff failed to find any plasma cells in the wall of the normal gallbladder or any glands in the region of the fundus. He described interruptions in the muscularis occupied by blood vessels of varying size and stated that strong contractions of the gallbladder force the mucosa through these interruptions or clefts, so that it may extend to the tunica fibrosa. These observations are illustrated by beautiful colored photomicrographs. He gave credit for describing the sinuses to Luschka, but I shall show later how many disagree with him. In continuing his observations, he stated that in cases of stones an active growth of the mucosa may be seen which has extended beneath the muscularis, the "cholecystitis glandularis proliferans" of Boyd.¹² These sinuses hinder contraction of the wall of the gallbladder, contain cellular debris, inflammatory cells and crystals and act as niches for the formation of stones.

Aschoff contended, and for his contention I shall offer confirmatory evidence later, that an abundance of these Rokitsansky-Aschoff sinuses is not the cause but the result of cholelithiasis, and, indeed, the result of increased pressure and the presence of stones complicated by infection. The sinuses constitute evidence of increased pressure; the gland

8. Mueller, Friedrich C.: Zur pathologischen Bedeutung der Drüsen in der menschlichen Gallenblase, Inaug. Dissert., Kiel, L. Handorff, 1895.

9. Létienne, A.: Des calculs pariétaux, *Méd. mod.* 6:529-531, 1895.

10. Péraire, M.: Calculs biliaires dans le canal cystique, *Rev. de chir.* 28: 41-62, 1903.

11. Aschoff, L.: Bemerkungen zur pathologischen Anatomie der Cholelithiasis und Cholecystitis, *Verhandl. d. deutsch. path. Gesellsch.* 9:41-48, 1905.

12. Boyd, W.: *Surgical Pathology*, Philadelphia, W. B. Saunders Company, 1933, p. 335.

formation indicates chronic infection. Such sinuses also play an active and important part in inflammatory processes and when filled with pus are apt to perforate.

Skikinami,¹³ in 1908 said that Aschoff first described these glands and that Luschka knew them only superficially; that to Aschoff should go the credit for describing their origin and development. He stated that Rokitansky-Aschoff sinuses are diverticula in the epithelium of the mucosa and that they are therefore always connected with the lumen of the gallbladder, though the indentations may reach well into the tunica propria.

Again, in "Die Cholelithiasis"¹⁴ Aschoff and Bacmeister gave Luschka all the credit for describing these sinuses, although they said that Skikinami was quite correct in stating that Luschka knew them only superficially. In this text are presented excellent drawings of intramural stones, which the authors contended were in Luschka's canals, although they were surrounded by fibrous tissue without a suggestion of mucosa.

Since Aschoff's original paper, there have been numerous reports of intramural gallstones. Rago¹⁵ and Grasso¹⁶ stressed their importance in relation to stones in the lumen; Grasso, in particular, emphasized the formation of intramural stones as a cause of cholelithiasis and presented diagrams to show stones being extruded into the lumen of the gallbladder.

Gosset and his co-workers¹⁷ gave an excellent description of the formation of intramural stones, with five illustrative plates. They found the stones always located in the interior of Rokitansky-Aschoff sinuses and removed them easily with the aid of small forceps. According to their description, the stones are surrounded by closely applied mucosa, but at times a small amount of mucous secretion is interposed. About the sinuses there is usually cellular reaction consisting of plasma cells and lymphocytes and rarely of polymorphonuclear leukocytes. The adventitia is usually scarred and fibrosed. The authors lead one to believe that intramural stones occur without the presence of free stones in the lumen and may, in fact, cause them. They advocate cholecystectomy as the only treatment which offers a cure.

13. Skikinami, J.: Beiträge zur mikroskopischen Anatomie der Gallenblase, Anat. Hefte **36**:554-597, 1908.

14. Aschoff, L., and Bacmeister, A.: Die Cholelithiasis, Jena, Gustav Fischer, 1909, p. 18.

15. Rago, G.: La calcolosi intramurale della cistifellea, Osp. maggiore **20**:453-464, 1932.

16. Grasso, R.: Considerazioni su di un caso di cistifellea a fragola e di calcolosi interstiziale, Policlinico (sez. chir.) **38**:335-350, 1931.

17. Gosset, A.: Duval, P.: Bertrand, I., and Montier, F.: Les calculs vésiculaires intramuraux, Presse méd. **11**:161-164, 1930.

In a recent article Baroni¹⁸ reported a case and discussed calculosis of the gallbladder with the production of calculi in the tissues of the organ without damage to the Rokitansky-Aschoff sinuses. In his opinion, the mechanism which produces calculosis is the same as that which causes "strawberry gallbladder," and he expressed the belief that the former constitutes the end-stage of this process (fig. 2).

The development of diverticula of the gallbladder arising from these sinuses is of interest in connection with this study. The subject was discussed by Vastine,¹⁹ who reported 2 cases diagnosed by roent-



Fig. 2.—Photomicrograph showing proliferation of the mucosa of the gallbladder beneath the muscularis, while to the side and entirely separate is a large deposit of cholesterol crystals; $\times 68$. These deposits are not surrounded by mucosa, but foreign body giant cells may be seen at the periphery. This condition has been described by Baroni (*Arch. ital. di anat. e istol. path.* 5:76-96, 1934).

gen examination. He expressed the belief that the diverticula are the direct result of sinuses. I have had the privilege of studying the sections from 1 of his gallbladders. Rokitansky-Aschoff sinuses and a diverticulum were present, but the latter was not lined with mucosa as one would expect it to be were it the result of a sinus. The hypothesis may be advanced that the stone has ulcerated part way through the

18. Baroni, B.: Sulla genesi interstiziale dei calcoli nella cistifellea, *Arch. ital. di anat. e istol. path.* 5:76-96, 1934.

19. Vastine, J.: Diverticulum of the Gallbladder, *Am. J. Roentgenol.* 31:603-606, 1934.

wall, forming the diverticulum by destruction of the mucosa and muscularis.

In 1894 Weltz²⁰ reported 5 cases of diverticula, all of which seemed to have been small and within the wall of the gallbladder. In his first case he found large cavities in the wall, which apparently had no connection with the lumen; one, however, communicated with the lumen, and he considered this a diverticulum. In the second case he found stones in the wall of the gallbladder, but he was unable to trace any connection with the lumen. These 2 cases seem quite definitely related to Rokitsansky-Aschoff sinuses; the other 3 probably are not so related, for in 1 the diverticulum was lined with muscularis and in the other 2 the mucosa was lacking.

Deaver and Ashhurst²¹ reported a case in their textbook in which the gallbladder was full of stones of various sizes. The neck of the gallbladder, just above the junction with the cystic duct, was pouched out in such a way as to form a sac which pressed on the common duct and caused obstructive jaundice. Cholecystectomy was done, and stones were not found in the common duct. Rokitsansky-Aschoff sinuses were not mentioned. In this case the sac may have been a dilated ampulla.

Bársony²² reported the case of a 23 year old woman with a diverticulum the size of a hazelnut, located at the fundus of the gallbladder and lined with mucous membrane. The diverticulum was diagnosed by roentgen examination. At operation stones were not found in the gallbladder.

ORIGINAL WORK

In this study 300 gallbladders removed at operation have been examined. In the majority of cases two sections were taken from each specimen, one from the neighborhood of the fundus and the other from near the neck. Particular attention was paid to the presence or absence of Rokitsansky-Aschoff sinuses.

In the normal gallbladder there is some invasion of the muscularis by mucosa, but so far no one has defined the dividing line between normal invasion and that type of herniation which has been called a Rokitsansky-Aschoff sinus. As a result of this study, I have defined a Rokitsansky-Aschoff sinus as a herniation or outpouching of the mucosa below or beneath the muscularis. Mucosal sinuses, lying entirely free beneath the muscularis and covered by intact muscle, are included in the definition, for serial sections show a communication between them and the lumen of the gallbladder.

20. Weltz, H.: Ueber Divertikel der Gallenblase, Inaug. Dissert., Kiel, L. Handorff, 1894, pp. 5-20.

21. Deaver, J. B., and Ashhurst, A. P. C.: Surgery of the Upper Abdomen, Philadelphia, P. Blakiston's Son & Co., 1914, p. 42.

22. Bársony, T.: Divertikel der Gallenblase, Klin. Wchnschr. 7:216-217, 1928.

With this as a standard definition, the 300 gallbladders were classified. In 101 (30 per cent) typical Rokitansky-Aschoff sinuses were found, while in 199 (60 per cent) they were absent.

The majority of writers have failed to stress the presence of gallstones as a factor in the formation of Rokitansky-Aschoff sinuses; rather, many of them have concluded that stones form in the sinuses, are extruded into the lumen and so give rise to gallstones in the gallbladder. Aschoff has, however, stressed the importance of gallstones



Fig. 3.—Photomicrograph showing a section from the neck of the gallbladder, with scattered muscular fibers; $\times 262$. This is a true gland in the region in which such glands are usually found. Note the tall columnar cells filled with mucus, the nuclei being pushed to the outside or bottom of the gland. The best description of these glands in an English text is by Maximow (*Textbook of Histology: True Ducts of Luschka*, Philadelphia, W. B. Saunders Company, 1931, p. 551).

as an etiologic factor in the formation of these sinuses, and my study on this relationship may here be stated.

In the 300 specimens reviewed, stones were found in the gallbladder in 231, or 77 per cent, and not found in 69, or 23 per cent. Of the 231 gallbladders containing stones, 98, or 42 per cent, showed Rokitansky-Aschoff sinuses, and 133, or 58 per cent failed to show them. Of the 69 gallbladders free from stones, only 3, or 4 per cent, showed Rokitansky-Aschoff sinuses, and 66, or 96 per cent, failed to show them.

In the total of 101 gallbladders which showed Rokitansky-Aschoff sinuses, 98, or 97 per cent, contained stones, and 3, or 3 per cent, failed to contain stones. This would certainly substantiate Aschoff's original contention, if such substantiation were needed (fig. 3).

In figures 4, 5 and 6 the development of Rokitansky-Aschoff sinuses is shown. The mucosa invaginates or grows completely through the muscularis and expands in the subserosa, leaving a neck which communicates with the lumen of the gallbladder. The epithelium may proliferate extensively outside the muscularis, giving rise to the "chole-



Fig. 4.—Photomicrograph showing the invasion of the mucosa to the lowermost level of the muscularis; $\times 59$. This has been set as a minimum requirement for the designation of Rokitansky-Aschoff sinuses. The mucosa is connected with the lumen of the gallbladder and has penetrated the entire muscular layer of the wall. As can be seen, a small amount of connective tissue has been carried through the wall by the mucosa, while lymphocytes infiltrating the surrounding tissue can be seen. This mucosa is intact, whereas much of that in the lumen is desquamated.

cystitis glandularis proliferans" of Boyd, and may appear to be completely cut off from the cavity of the gallbladder (fig. 6). As asserted by Aschoff, there is a definite tendency for the evagination of the mucosa to occur at points where large vessels penetrate the muscularis, but this is not always true. Halpert,²³ who studied over 300 gall-

23. Halpert, B.: Morphological Studies of the Gallbladder, Bull. Johns Hopkins Hosp. 41:77-103, 1927.

bladders removed at operation, found that the muscularis of the healthy gallbladder under ordinary conditions is dense enough to prevent out-pouchings of the mucosa toward the external layer. He expressed the belief that the normal defects in this layer which serve for the passage of blood vessels may also occur independently and offer potential channels through which, under certain circumstances, the mucosa may protrude toward the external layer. He found that the presence of typical and numerous Rokitansky-Aschoff sinuses is usually associated with structural changes in the wall of the gallbladder, which may be



Fig. 5.—Photomicrograph showing the growth of the mucosa through the wall in the direction of the vessels; $\times 81$. Two arteries with an accompanying thin-walled vein may be seen. These vessels appear to be attracting the mucosa. Notice again the increase of fibrous tissue and infiltration by lymphocytes about the sinus.

responsible for their formation. Most constant and conspicuous of these are the thickening of the wall of the viscus, due to the marked hypertrophy of the muscularis and increase of the connective tissue forming the perimuscularis and a varying degree of cellular infiltration in the subepithelial layer, the intermuscular septums and the perimuscular layer and especially around the fundi of the Rokitansky-Aschoff sinuses. In Halpert's article no mention is made of the relation of Rokitansky-Aschoff sinuses to stones or their incidence in the gallbladders studied.

The histories of all patients with gallstones in this series have been reviewed with regard to the length of time elapsing between the onset

of symptoms presumably due to a pathologic process in the gallbladder and the operation.

In the case of 98 gallbladders with stones and Rokitansky-Aschoff sinuses this period averaged forty-eight and fifteen hundredths months, or a little over four years. For the 133 gallbladders which showed stones but in which there were no Rokitansky-Aschoff sinuses, the average time from the onset of symptoms to operation was forty-seven and ninety-three hundredths months, or just short of four years. These facts seem to show conclusively that the duration of the disease has little or nothing to do with the formation of these sinuses.

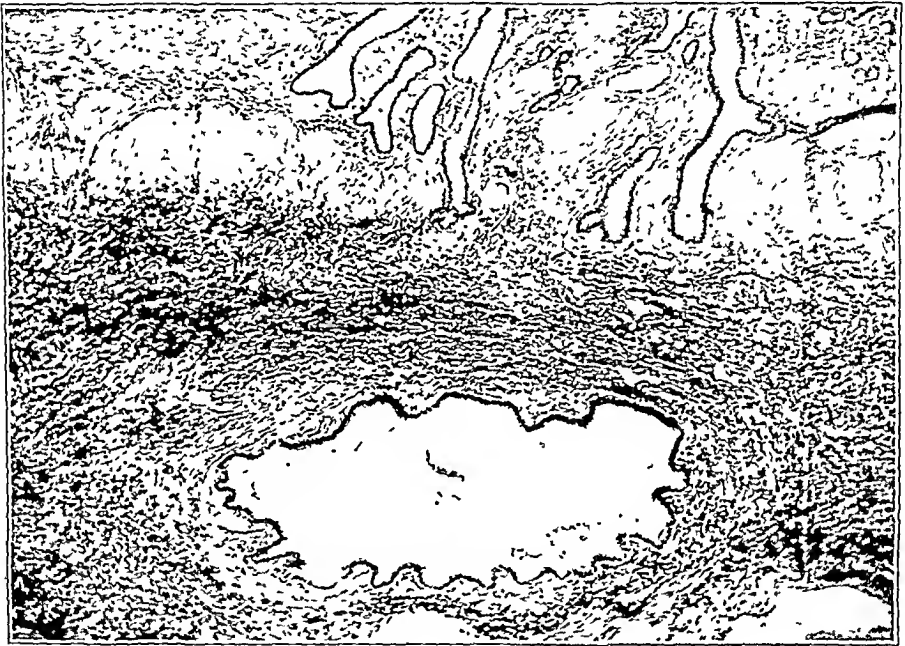


Fig. 6—Photomicrograph showing the mucosa growing completely through the muscularis, beneath which is a large space lined by mucosa; $\times 48$ This space appears to be cut off from the cavity of the gallbladder. In other sections this is found to communicate with the lumen. Note the dense connective tissue infiltrated by lymphocytes surrounding this area.

COMMENT

After the formation of a Rokitansky-Aschoff sinus, what may be its course?

1. It may remain stationary.
2. It may produce "cholecystitis glandularis proliferans."
3. It may develop into a diverticulum.
4. It may form an abscess and perforate.
5. Stones may form in its interior.

Owing to the large number of gallbladders in which these sinuses are found and the small number in which complications occur, it would seem that the large majority of sinuses remain stationary, or at least inactive.

Although fairly common, "cholecystitis glandularis proliferans" does not appear to lead to a serious pathologic process, though it may bear a relationship to carcinoma, which occurs almost entirely in gallbladders harboring stones.

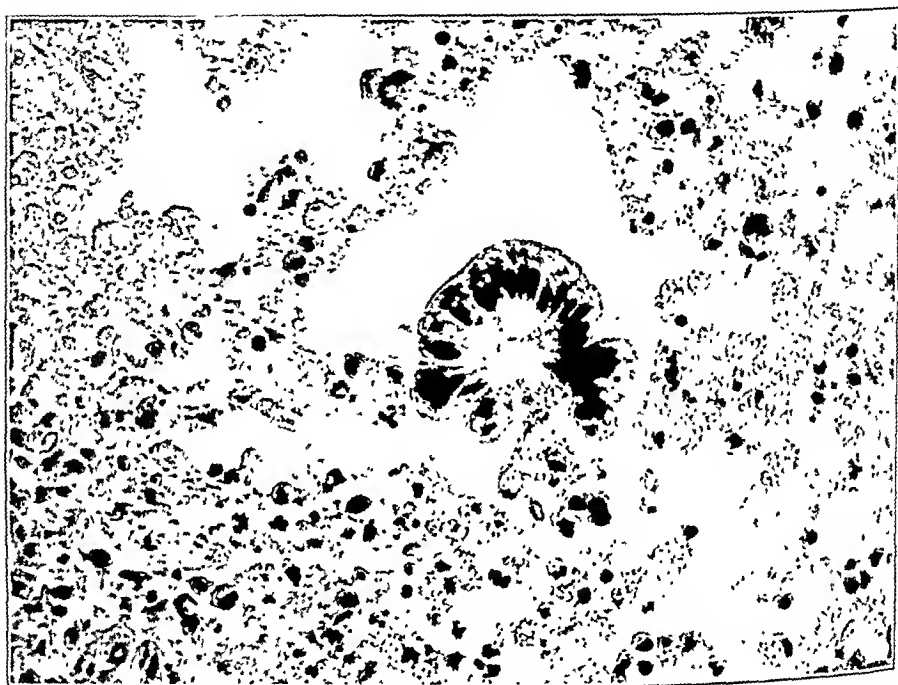


Fig. 7.—Photomicrograph showing a bit of well preserved mucosa of the gallbladder lying in an abscess which has formed entirely beneath the muscularis; $\times 350$. In this gallbladder there were five abscess cavities lying in the wall. One had ruptured by means of a punched-out defect in the wall of the gallbladder beneath the liver and had formed an abscess there, while the others drained into the gallbladder. Rokitansky-Aschoff sinuses were present, and it seems that the inflammation started in these and developed into abscesses; all but one drained back into the gallbladder; the other perforated through the wall.

It has been stated that diverticula of the gallbladder occur in rare instances. In the opinion of some observers, they are the result of Rokitansky-Aschoff sinuses.

In his original article, Aschoff called attention to the presence of abscesses arising from the sinuses in the wall of the gallbladder and showed that there is much more inflammation surrounding the sinus than elsewhere in the wall. In 2 of our cases there was a small punched-out perforation in the wall without extensive damage elsewhere. In

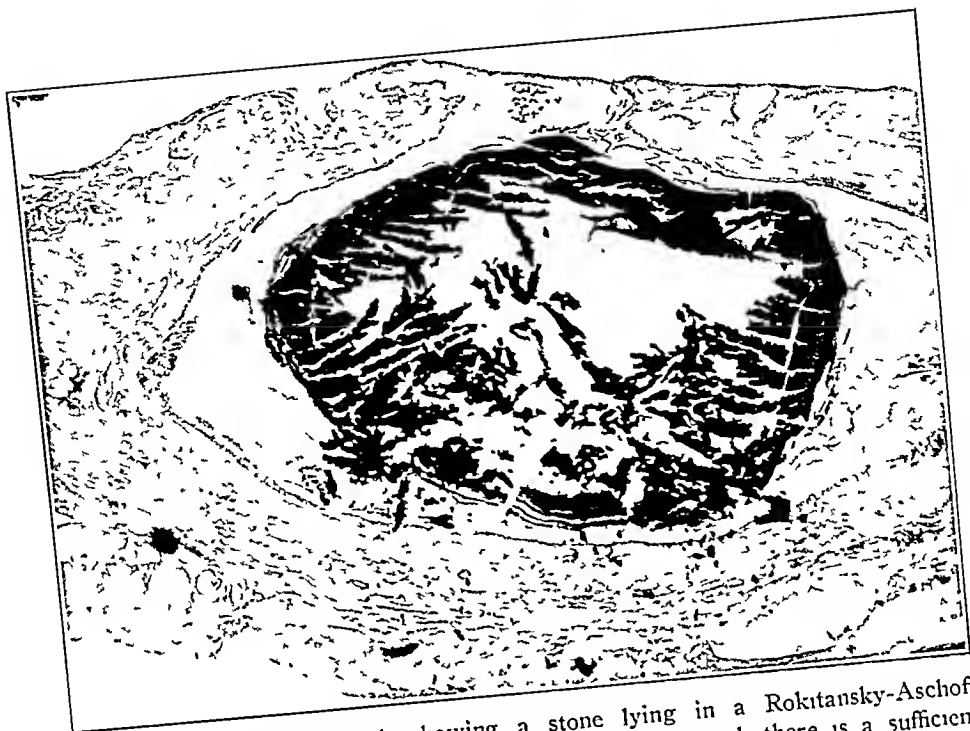


Fig 8—Photomicrograph showing a stone lying in a Rokitansky-Aschoff sinus; $\times 30$. Although the mucosa is largely desquamated, there is a sufficient amount left to show that the stone had been entirely surrounded by it. An opening may be seen leading into the lumen of the gallbladder. Such an opening has led various investigators to believe that stones formed in the sinuses and were extruded into the cavity of the gallbladder.

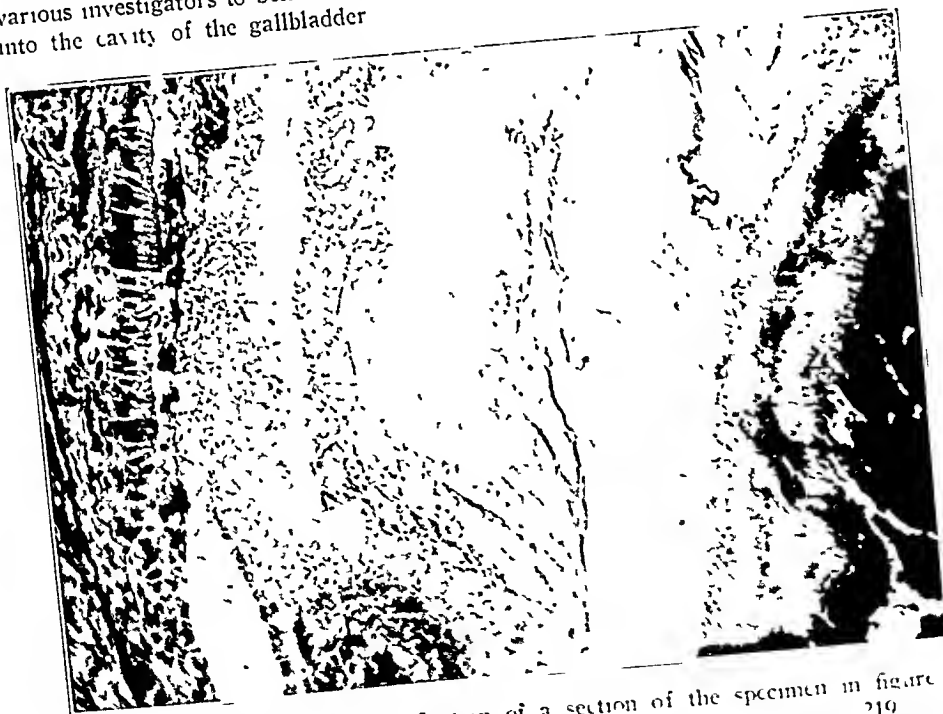


Fig 9—High power magnification of a section of the specimen in figure 8 to show the epithelium lining the sinus and its relation to the stone.

both cases, Rokitansky-Aschoff sinuses were found. In 1 the perforation had formed an abscess between the gallbladder and the liver, while in the wall of the gallbladder there were four other abscess cavities opening into its lumen. In one section (fig. 7) fragments of the mucosa of the gallbladder were present in the midst of purulent exudate. It would seem that in both of these cases perforation was secondary to an infection of the Rokitansky-Aschoff sinuses.

The formation of stones in the sinuses seems less important than abscess formation and perforation. In several instances, granular and cellular debris and bile pigments have been found in the sinuses; 1 gallbladder in the series which contained 40 black faceted stones in its lumen showed many small concretions, from 2 to 4 mm. in diameter, embedded beneath the mucosa (figs. 8 and 9). On section these stones appeared to be composed of inspissated bile pigments. They lay in Rokitansky-Aschoff sinuses, which were lined with cuboidal epithelium. Around the stones there was mucinous material, and outside the sinus, marked infiltration of lymphocytes.

SUMMARY

Stones within the wall of the gallbladder were first described by Morgagni and later by Rokitansky, who found them in small outpocketings in the mucous membrane of the wall. These sinuses were first studied and described in full by Aschoff. They are known as Rokitansky-Aschoff sinuses. Aschoff also called attention to stones in the sinuses, to the marked infection which may surround them and to abscess formation and perforation which may occur. He advanced the theory that the sinuses are the result of increased pressure and stones within an infected gallbladder. Many observers since Aschoff have reported these sinuses, but for the most part they have failed to associate their presence with stones in the gallbladder; some have even considered them the cause of cholelithiasis. They also have been believed to be factors in the development of diverticula, and their multiplication under the muscularis is defined as "cholecystitis glandularis proliferans."

Rokitansky-Aschoff sinuses have been accurately defined, and a report is made on 300 gallbladders removed at operation and studied by me. Of this number 231, or 77 per cent, contained stones, while 101, or 30 per cent, showed Rokitansky-Aschoff sinuses. Of the 101 gallbladders in which sinuses were found, 98, or 97 per cent, contained stones.

Two cases are described in which the gallbladder had perforated: in both of these, Rokitansky-Aschoff sinuses were present and were thought to have played a part in the perforation. One case is reported in which there was formation of stones inside the sinuses, lying deep beneath the muscularis of the gallbladder.

CONCLUSIONS

Rokitansky-Aschoff sinuses are found to be not uncommon when the walls of gallbladders are studied microscopically.

The sinuses are the result of cholelithiasis and secondary infection rather than the cause of gallstones.

Rokitansky-Aschoff sinuses may give rise to local abscess formation in the wall of the gallbladder. The abscesses may drain into the lumen or perforate through the wall of the gallbladder.

Stones may form within the sinuses, and at operation they will be found to lie under the muscularis.

DRAINAGE OF CEREBROSPINAL FLUID IN THE TREATMENT OF ACUTE HEAD INJURIES

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The treatment of acute head injuries has recently become of increasing importance, owing primarily to the increasing incidence of the disease and secondly to the prevalence of the postconcussion syndrome, particularly in cases in which the patient is seeking compensation.

Much has appeared in the literature on treatment, and in regard to most points the authors agree. Concerning rest, sedatives, the application of ice to the head and the restriction of fluid, there is little disagreement.

However, regarding the use of spinal puncture and the indications for surgical intervention, there have always been differences of opinion among neurosurgeons and confusion in the minds of the general surgeons, who see most of the patients with such injuries. There have always existed differences of opinion regarding the use of spinal puncture and surgical treatment in cases of head injury, but recently there has been more confusion by the appearance of articles of wide-reaching influence (Dandy¹) in which the use of both spinal puncture and the administration of hypertonic solutions intravenously is strongly deplored and the impression is given that little is to be done for the patient other than to prescribe rest, operation being reserved for the small group (10 per cent) who do not die immediately and who fail to respond favorably to rest alone.

I propose to show in this article that much can be done in the treatment of patients with acute head injuries, including those with only mild concussion, and particularly that drainage of cerebrospinal fluid, both by lumbar puncture and by subtemporal trephine, but especially by the former method, is not only without danger but highly beneficial.

Clinical, pathologic and surgical observations all point to an increase of intracranial pressure as the outstanding finding in cases of cerebral concussion and to an excessive secretion of the cerebrospinal fluid as the principal factor causing this pressure. It would therefore seem reasonable that the most logical and convenient method of decompression or of returning intracranial pressure to normal would be drainage of the cerebrospinal fluid. This may be done in two ways: (1) by

1. Dandy, W. E.: *Diagnosis and Treatment of Injuries of Head*, J. A. M. A. **101**:772 (Sept. 2) 1933.

repeated spinal puncture and (2) by subtemporal trephine or decompression with drainage. The former method is by far the most frequently used; the latter is indicated in less than 10 per cent of the cases. Cisternal puncture is a more dangerous procedure and has little advantage over lumbar drainage.

It is decompression by drainage of the cerebrospinal fluid to which I would first direct attention. I first used this procedure with caution, in view of the consensus of many authors that spinal puncture is dangerous in states of increased intracranial pressure. However, it was reasoned that there should be no herniation of the medulla and cerebellum when the increased pressure is due to a fluid mass which could be drained around the brain stem through the basilar cisterns. This supposition was borne out clinically in a study of over five hundred punctures by the frequent and prompt relief of pressure symptoms after spinal puncture and the total absence of any untoward results.

Fourteen patients were subjected to craniotomy for the purpose of removing clots or fluid; on these, preoperative and postoperative spinal punctures were done, and the underlying pathologic process was determined at operation or at autopsy.

In the series of cases reported herewith, spinal puncture was done on every patient having sustained any degree of concussion who was having even minor pressure symptoms, i. e., headache, nausea, vomiting, stupor or coma, particularly if there was an associated bradycardia. The puncture was repeated every twelve to twenty-four hours as the symptoms indicated; in the average case it was repeated every day until the initial pressure was approximately normal (from 80 to 150 mm.); in the more serious case associated with deep coma or severe and unrelieved headache and vomiting, drainage was repeated as often as every six to eight hours.

The clinical results will be described later. Briefly, there was definite improvement in all symptoms after the first few punctures and frequently after the first puncture. On the whole, headache disappeared even before the pressure became normal; consciousness and rationality returned in most cases when the pressure became normal. In every case (with one exception) there was progressive clearing of the bloody fluid. Frequently, before the pressure had returned to normal, the spinal punctures were discontinued for some reason. I choose to call this period in which no drainage was done the "no drainage interval." The patients nearly always suffered a return of pressure symptoms, and on subsequent puncture the pressure would be found secondarily elevated. I choose to call this elevation the "secondary rise." Occasionally, on the first puncture, particularly if done early, the pressure would be approximately normal, but after several days without

spinal punctures pressure symptoms would develop, and on the next puncture the spinal pressure would be high; subsequently, the symptoms were relieved by drainage.

Occasionally a patient would continue to have high pressure and unrelieved symptoms even after repeated drainage. I choose to call this type of pressure "sustained pressure." In these cases it was assumed that there were accumulations of fluid subdurally (extra-arachnoid) which were loculated and could not be drained through the sub-arachnoid system. Here surgical measures were indicated for drainage of the loculated fluid. However, the same overproduction of cerebro-spinal fluid continued, and further spinal punctures were necessary to control the pressure after the drainage of fluid subtemporally had ceased and the wound had healed.

After carrying out this treatment in about one hundred and forty cases of head injury without any guide other than the patient's clinical signs and symptoms, it was found that the clinical course closely paralleled the degree of pressure of the intracranial fluid, as shown by the curves for the spinal fluid pressure. The curves formed by these initial pressures fell into three well defined types: (1) a progressive fall in pressure, (2) a secondary rise in pressure after a "no drainage interval" and (3) sustained pressure.

The excellent results and the freedom from complications obtained in this series of patients by the use of spinal puncture compared with the adverse criticism of this procedure in the recent literature makes it obvious (1) that either there is or there is not a place for lumbar drainage in at least certain selected cases; (2) that the question is vitally important, if the surgeon is to have a clear idea of the treatment of head injuries, and finally, (3) that the solution of the problem should be based on clinical observations and findings in a sizable group of cases.

The points to be considered are: drainage by spinal puncture, its dangers, diagnostic value and therapeutic value, and drainage by subtemporal decompression, its indications, and preoperative and post-operative spinal drainage.

REVIEW OF THE LITERATURE

A perusal of the literature will emphasize the discord which exists even among reputable neurosurgeons.

SPINAL DRAINAGE

Dangers.—Dandy² stated that "in the presence of intracranial pressure from whatever source, lumbar punctures are always dangerous."

2. Dandy, W. E.: Treatment of Acute Intracranial Pressure, in Lewis, Dean: Practice of Surgery, Hagerstown, Md., W. F. Prior Company, Inc., 1932, vol. 12, chap. 1, p. 284.

On the other hand, Grant³ said that he had "never seen properly performed lumbar puncture have any ill effect," and Jackson⁴ expressed the belief that the "danger of lumbar puncture in these acute traumatic cases has been greatly overestimated." According to Jaeger⁵: "This method of treating brain injuries is too dangerous—its possible good effects being far outweighed by the harm it can do by medullary compression and trauma." On the other hand, Bagley⁶ stated that "when there is an excess of cerebrospinal fluid, a lumbar puncture is not dangerous but offers relief." Furthermore, Morrissey⁷ and Towne⁸ both mentioned the safety and desirability of doing early and repeated spinal drainage. McCreery and Berry⁹ said: "We believe that this danger has been over-emphasized and that the advantages to be gained—both diagnostically and therapeutically—outweigh the risks."

There are those who use lumbar puncture but still have some question regarding the danger. Rand and Nielsen¹⁰ reported that they have had no untoward results from lumbar puncture, yet they watch the pulse and the general condition of the patient closely. McKenzie¹¹ advised slow withdrawal of fluid but stated that it is possible to remove too much fluid and so bring about herniation of the medulla and cerebellum into the foramen magnum. Naffziger¹² said that a direct reading of the intracranial pressure by the spinal fluid manometer was often impracticable owing to the frequency of irritability, restlessness and lack of control of the patient. Cairns¹³ stated that lumbar puncture "is open to the objection that it disturbs the patient

3. Grant, F. C.: Treatment of Cranial Trauma, *S. Clin. North America* 5: 1537 (Dec.) 1925.

4. Jackson, Harry: The Management of Acute Cranial Injuries by the Early, Exact Determination of Intracranial Pressure, and Its Relief by Lumbar Puncture, *Surg., Gynec. & Obst.* 34:494, 1922.

5. Jaeger, J. R.: Treatment of Injuries to Skull and Brain, *Colorado Med.* 28:348, 1931.

6. Bagley, Charles, Jr.: Blood in Cerebrospinal Fluid: Resultant Functional and Organic Alterations in Central Nervous System; Clinical Data, *Arch. Surg.* 17:18 (July) 1928.

7. Morrissey, E. J.: Head Injuries: Their Treatment, *California & West. Med.* 35:198, 1931.

8. Towne, E. D., in discussion on Morrissey.⁷

9. McCreery, J. A., and Berry, F. B.: A Study of Five Hundred and Twenty Cases of Fracture of the Skull, *Ann. Surg.* 88:890, 1928.

10. Rand, C. W., and Nielsen, J. M.: Fracture of the Skull: Analysis of One Hundred and Seventy-One Proved Cases, *Arch. Surg.* 11:434 (Sept.) 1925.

11. McKenzie, K. G.: The Management of Cranio-Cerebral Injuries, *Univ. Toronto M. J.* 6:215 (May) 1929.

12. Naffziger, H. C.: Head Injuries: Indications for Surgical Treatment, *S. Clin. North America* 3:699, 1923.

13. Cairns, Hugh: Treatment of Head Injuries: II. Conservative and Operative Measures, *Lancet* 1:617 (March 24) 1928.

considerably, and for this reason, whenever possible, the use of hypertonic salt solutions is to be preferred."

There is also confusion concerning the degree of intracranial pressure in which puncture is indicated. Sharpe¹⁴ stated that it is only for patients having a mild increase of intracranial pressure that this method should be advocated as ". . . patients having a high increase of intracranial pressure (over 16 mm. of mercury) should not be subjected to the risk for fear that this high intracranial pressure would force the medulla into the foramen magnum. . . ." Peet¹⁵ stated that although there was danger of increasing hemorrhage, he did use the method early in cases of acute involvement to protect the medulla! It is no wonder that surgeons are confused with such conflicting statements in the literature.

Diagnostic Value.—As a diagnostic measure, the advisability of the use of lumbar puncture is still undecided. According to Dandy² spinal punctures do not yield any information of value in diagnosis and the information obtained by carefully studying the patient's signs and symptoms is far better and at the same time is more safely secured. He also stated that spinal puncture and the injection of dextrose intravenously are contraindicated and may cause serious harm. Coleman¹⁶ wrote: "We have used spinal puncture guardedly in the examination of patients with acute brain injury severe enough to require treatment directed to the intracranial condition." The proper use of spinal puncture gives added information, not supplied clinically, as to the degree of intracranial pressure.

McCreery and Berry⁹ stated that were it not for the information gained by spinal tapping some patients, whose injury was relatively slight and whose symptoms were evanescent, would be thought to have merely a mild concussion.

Therapeutic Value.—As a therapeutic measure, the discussion of lumbar puncture occupies the center of the stage. Dandy² stated: "How certain is it that there may not be adverse effects, either immediate or remote . . .? On the next puncture the period of relief may be shorter and each succeeding puncture has less, and finally no effect; . . . spinal punctures and intravenous injections of hypertonic glucose or sodium chloride are contra-indicated in efforts to reduce

14. Sharpe, William: *Diagnosis and Treatment of Brain Injuries*, Philadelphia, J. B. Lippincott Company, 1920, p. 81.

15. Peet, Max M.: *Reduction of Increased Intracranial Pressure by Intravenous Administration of Glucose and Hypertonic Ringer's Solution*, J. A. M. A. **84**:1994 (June 27) 1925.

16. Coleman, C. C.: *The Management of Acute Brain Injuries*, J. A. M. A. **97**:1696 (Dec. 5) 1931.

the intracranial pressure. They may cause serious harm." Wilensky¹⁷ said that "spinal puncture has not given complete satisfaction as a therapeutic measure and that "the ultimate result has not differed from that obtained when no such procedure was used." Naffziger¹² stated that "in the face of rapidly advancing signs of pressure spinal puncture is inadequate." Glaser,¹⁸ in a discussion of Morrissey's article, said:
 . . . I have reduced the use of spinal puncture to a minimum.
 . . . In my experience, cases do well without this form of treatment." On the other hand, Adson¹⁹ expressed the belief that if other measures fail to reduce the pressure "spinal puncture should be performed every eight to twelve hours." According to Cairns,¹³ the fluid should be withdrawn slowly; while Coleman¹⁶ stated that spinal puncture is of more value as a test for pressure than as a therapeutic measure.

Other writers have been enthusiastic concerning the use of spinal punctures as a therapeutic measure. McCreery and Berry⁹ stated: "In the more severe cases repeated spinal taps have been the most valuable method of treatment. Henry²⁰ reported the use of repeated spinal punctures "in the absence of coma, focal signs or obvious fracture. . . . this is repeated in four, eight or twelve hours, and as often as deemed necessary to keep the pressure down to normal for several days." He further stated that ". . . operation has been done much less frequently since adopting this measure. . . ." Jackson⁴ also reported the uses of this measure. He stated: "The relief of increased pressure on the brain and the re-establishment of the normal path of absorption of the cerebrospinal fluid can be obtained by repeated lumbar drainage." Mock expressed the belief that the mortality has decreased with the use of lumbar drainage and the injection of hypertonic solutions. Johnson²¹ also reported the use of repeated punctures.

Rand and Nielsen¹⁰ said that drainage of cerebrospinal fluid is often resorted to as a therapeutic measure, especially in cases in which the pressure is increased, and that those patients in whom headache is relieved may be benefited if this procedure is repeated. They stated: "It appears that more prompt relief is obtained from repeated lumbar puncture than from other methods."

17. Wilensky, A. O.: The Neurologic Manifestations of Fracture of the Skull (Craniocerebral Injuries), *S. Clin. North America* 1:1709, 1921.

18. Glaser, in discussion on Morrissey.⁷

19. Adson, A. W.: Treatment of Injuries to the Head, *Internat. J. Med. & Surg.* 43:617, 1930.

20. Henry, C. K. P.: Cranial and Intracranial Injuries, *Canad. M. A. J.* 15: 913, 1926.

21. Johnson, L. W.: Treatment of Head Injuries, *U. S. Nav. M. Bull.* 29: 592, 1931.

Drainage of Bloody Fluid.—Rand and Nielsen¹⁰ found blood in the cerebrospinal fluid of 85 per cent of patients with fractures, and Werden²² found the same percentage in all patients with concussion.

That the cerebrospinal fluid contains blood which is irritating to the meninges and may cause additional pressure there is no doubt. However, here again writers differ on the treatment of traumatic hemorrhage in the subarachnoid system. Dandy² has been the most emphatic in stating that the additional space afforded by drainage permits renewed bleeding and that the only hope of cessation of hemorrhage is by compression of the brain against the bleeding point. Coleman¹⁶ said that it is doubtful if any considerable amount of blood can be removed by spinal puncture, and Bagley⁶ stated that occasionally the fluid became more bloody and that there was a question if lowering the pressure did not precipitate more hemorrhage, although in another article he said that bloody fluid can be drained by repeated puncture and that subtemporal drainage is advisable in the majority of cases and absolutely necessary in some. Peet¹⁵ said that there was danger of increasing the hemorrhage but that he did use spinal puncture early in cases of severe involvement to protect the medulla. Rand and Nielsen¹⁰ said that patients with bloody spinal fluid present signs and symptoms of meningitis, which disappear after the blood had been absorbed or drawn off by repeated punctures.

Surgical Drainage.—Even more has been written concerning subtemporal decompression in cases of head injury. It goes without saying that extradural and subdural hematomas are definitely surgical lesions. In this article I am interested in subtemporal decompression only from the point of view of establishing drainage in cases of increased intracranial pressure from excessive subdural and subarachnoid free fluid. The literature on this point is in considerable variance and discord, and even Dandy²³ stated that "it is here that the greatest differences in treatment are in vogue." It is his contention that no patient with a head injury, aside from one with extradural hematoma, should have treatment other than rest until he recovers spontaneously or the intracranial pressure increases to such a point that there is medullary decompensation and death is impending. He further stated that signs of this advancing medullary failure are deepening coma, restlessness, involuntary micturition or defecation and an increase in the temperature, and pulse and respiratory rates. Opposing this point of view, Jackson⁴ stated that to wait for these signs before intervention is to court disaster.

22. Werden, D. H.: *Craniocerebral Injuries: Study of One Thousand Two Hundred Cases*, California & West. Med. **37**:226, 1932.

23. Dandy.^{1, 2}

Of particular note, and expressing a view to which I take exception, is the statment of Dandy: "During the period of bradycardia there is usually no need for action. With the onset of the above signs of medullary failure, subtemporal decompression is indicated; this occurs in about 10 per cent of all cases. Another group of 20 per cent will succumb regardless of what is done." Thus there remains a group of patients, comprising 70 per cent of those with head injuries, for whom nothing is done to relieve the pressure. It is toward those patients for whom no treatment is supposedly indicated and those in whom signs of medullary failure are eminent that I would most earnestly direct attention.

A further perusal of the literature regarding surgical treatment for head injuries will give a better understanding of the subject. Jackson⁴ stated: "Lumbar drainage is superior to subtemporal decompression in relieving pressure below the tentorium cerebelli, and has the further advantage that it leaves no mutilating skull defect." He further stated that in experiments on dogs with increased pressure it is shown that pulse, respiration and blood pressure are affected only when the medulla is compressed and that "to wait for these changes as an indication for operation on the cerebrum in acute cranial injury is to court disaster." Rand and Nielsen¹⁰ wrote: "Occasionally we have resorted to decompression when the patient was exceedingly irritable and disoriented, provided lumbar puncture and dehydration had failed to give relief." Naffziger¹² expressed the belief that for the edematous brain, decompression is not satisfactory, for fluid must be removed in order to give relief, but he further added that in the face of rapidly advancing signs of pressure, spinal puncture is inadequate, and a dextrose solution is of no demonstrable value. Coleman¹⁶ reported the use of both spinal puncture and subtemporal decompression, but he appeared to favor the latter. He stated: ". . . so far as I know it has never been asserted that the repeated removal of spinal fluid at lumbar puncture and the administration of hypertonic solutions and magnesium sulphate will maintain continuously a lowered pressure," and "palliative measures . . . cannot be substituted for subtemporal decompression with drainage in all cases of brain injury."

Towne also reported the use of both procedures. He stressed particularly trephining for the drainage of subdurally trapped fluid and stated that he did not hesitate to do an exploratory operation in cases in which the differential diagnosis between cortical laceration and hemorrhage is difficult.

After having cared for three thousand, five hundred patients with head injury, I am convinced that decompression by repeated lumbar

punctures is definitely of value in a large majority, other than those with localized hematoma; that spinal drainage is indicated both preoperatively and postoperatively for those on whom surgical treatment is used (except those with hematoma) and finally that both spinal drainage and earlier surgical intervention are imperative for the group of 10 per cent (Dandy) in whom medullary failure is eminent. It is hoped that the following case reports will substantiate this contention.

SPINAL DRAINAGE

INDICATIONS

In this communication spinal drainage is not being offered as a universal remedy for cerebral concussion. It is offered as an adjunct to other equally important measures, of which little more than mention will be made in this article. Drainage of cerebrospinal fluid is stressed because it is this measure concerning which there is so much difference of opinion.

Contraindications will be discussed, but barring these, it may be said that drainage of cerebrospinal fluid is indicated in nearly every patient with concussion who shows (1) signs or symptoms of cerebral pressure. (i. e., varying degrees of coma, headache, nausea or vomiting, bradycardia and continued high cerebrospinal fluid pressure)—this holds also for postsurgical drainage—and (2) signs of meningeal irritation (i. e., cervical anteroposterior rigidity and continued bloody spinal fluid). Surgical drainage is indicated in patients who are not progressing well under spinal drainage, and it should not be delayed too long after the indications present themselves.

CONTRAINDICATIONS

There are certain well defined contraindications to lumbar puncture. Obviously the first is initial shock which follows injury. The next is extradural (arterial) hemorrhage. There is a tendency for this bleeding to be spontaneously retarded by pressure from cerebral edema. However, this pressure is often slight owing to the fact that blows which produce laceration of the middle meningeal artery are often minor and cause little cerebral damage and resultant edema. In any event, even marked cerebral pressure is almost never sufficient to control arterial bleeding. Spinal puncture is therefore contraindicated in that it lessens this retarding pressure.

The other less positive contraindication is compound fracture of the skull. If the fracture is in the vault, it is a depressed fracture subjacent to laceration of the scalp. Such a fracture does not positively contraindicate spinal drainage, but if the intracranial pressure is not endanger-

ing life it is better to postpone drainage until arachnoidal adhesions have walled off the potential entrance of infection. If the compound fracture is in the base (as are nearly all fractures which give rise to ecchymotic orbital lids, epistaxis, nasal cerebrospinal rhinorrhea, aural bleeding and cerebrospinal otorrhea, and perhaps also those which give rise to Battle's sign), it is again possible that drainage of cerebrospinal fluid may tend to diffuse infection from these sources into the subarachnoid system.

Continued drainage of cerebrospinal fluid from the nostrils and external auditory canals may so spontaneously decrease intracranial pressure that the patient is relieved of symptoms, and lumbar drainage does not become necessary. On the other hand, should pressure symptoms persist, even with rhinorrhea and otorrhea it may be that continued intracranial pressure is keeping the compound fracture and arachnoid tears open, in which case cautious and slow drainage of the spinal fluid would be indicated to assist in decreasing the pressure and hasten closure of the wound by arachnoidal or dural adhesions.

Some writers would include subdural hematoma among the contraindications to spinal puncture on the basis that medullary herniation would result. It is my experience that patients with subdural hematoma do not collapse after spinal drainage but in fact are temporarily much improved. This is reasonable in view of the fact that a fluid mass such as hematoma, when acute, arises from venous bleeding, which soon ceases, and when subacute or chronic, increases in size either from slow capillary bleeding or by osmosis of free spinal fluid. Therefore, when either acute or chronic, release of pressure cannot increase the size of the mass. Furthermore, there is frequently a diffuse subarachnoid and extra-arachnoid excess of free fluid accompanying the hematoma. When puncture is done, this fluid is drained around the brain stem, thus preventing medullary herniation. However, given a patient in profound coma with slow pulse and stertorous respiration already showing signs of medullary herniation and impending collapse, fluid may not be able to flow around the brain stem, and puncture would obviously be fatal. In such a case caffeine and a 50 per cent solution of dextrose injected intravenously and immediate trephining to establish drainage would be the only recourse.

SPINAL PUNCTURE FOR DIAGNOSIS

I agree with other writers that in many instances spinal puncture is not necessary to diagnose the presence of intracranial pressure and that its presence can be suspected by the clinical signs. However, there are cases in which the signs and symptoms were not present, yet on puncture the pressure was high. These are the cases in which as a rule

no treatment is given, but in which treatment should be continued to abort later pressure symptoms and sequelae.

On the other hand, I have seen occasional cases of profound coma from cortical lacerations in which for some reasons cerebral edema and an increased secretion of cerebrospinal fluid did not result and the spinal pressure remained normal. It is obvious that in these cases, though coma and even localizing signs persisted, surgical intervention would have been urged had not low spinal fluid pressure shown that a surgical, pressure-producing lesion did not exist.

The following case reports show that clinical improvement parallels pressure and that an elevated pressure calls for successive punctures until the pressure persistently remains normal or until a surgical lesion is successfully treated.

TECHNIC FOR SPINAL PUNCTURE

Punctures were done with the patient flexed in a horizontal posture. A 1 per cent solution of procaine hydrochloride was used locally in the skin and deep fascia and an 18 gage needle was employed. As soon as fluid was encountered, a glass adapter was inserted; this in turn was attached by 4 cm. of soft rubber tube to a straight glass tube with a 1 mm. bore, measuring from 450 to 500 mm., and marked at intervals of 50 mm. Usually but 0.5 to 1 cm. of fluid was lost during the connection. Fluid was allowed to run to the end of the manometer leveled into the horizontal or inclining position. The manometer was raised to the vertical position, and the initial pressure was taken; readings were made after the withdrawal of each 4 to 6 cm. of fluid. If no changes were observed in the pulse rate or quality and no complaints were elicited from the patient, the pressure was lowered to from 50 to 100 mm. regardless of the amount of fluid required. The final pressure and the total amount of fluid removed were observed and recorded together with its color and appearance, and after standing from twelve to twenty-four hours, the percentage of blood by volume.

GROUP A: PROGRESSIVE FALL OF PRESSURE

The largest group of patients (group A) was composed of persons in whom there was an average progressive fall in cerebrospinal fluid pressure on each successive puncture (charts 1 to 4). The group illustrates the course in the average patient who is adequately treated and the desired end-result to be obtained by such treatment. The patients in this group appeared to have fewer pressure symptoms, complications and sequelae and a shorter duration of illness. The average of the initial pressures found on the first punctures was 324 mm., while the average of the initial pressures obtained on the last puncture done was 167 mm., showing a definite decline to approximately normal during the course of treatment. That there was a corresponding improvement in clinical symptoms will be shown later.

There were twenty-nine patients in this group who had from three to eleven punctures each (average five). They were divided into (1) those in whom drainage was started early (within one or two days of the injury) and (2) those in whom treatment was delayed for from four to eight days.

Subgroup 1: Drainage Early, First or Second Day.—There were twenty-one patients in whom spinal drainage was done within the first or second day after injury and repeated nearly every day until the final pressure was within normal limits. In all patients the initial puncture showed a high pressure; in nearly every case there was a progressive decline in pressure on each succeeding puncture. There was often marked improvement in the degree of consciousness or in the severity of pressure symptoms after the first drainage, and in every case there was definite

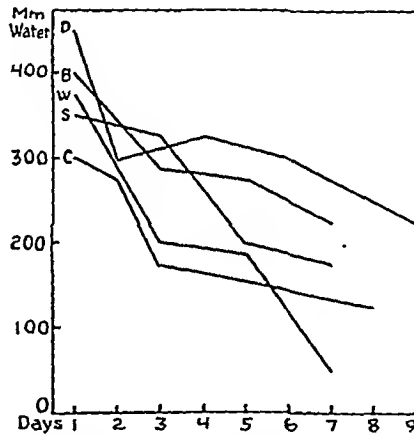


Chart 1.—Curves (designated by the initial of the patient) showing the progressive fall in the spinal fluid pressure of patients on whom drainage was done within the first or second day after injury. S indicates the curve for the patient in case 2.

improvement by the time the pressure had approximated normal. With one exception it was possible to control headache, so that by the time the patient was ready for discharge in from ten to fifteen days he was entirely free from symptoms. In the one exception, although the pressure decreased, coma persisted, and a subtemporal drainage was necessary.

The following cases (charts 1 to 3), with findings arranged so as to give the dates of symptoms, the initial spinal fluid pressure, the amount of fluid removed and the condition of the fluid, are representative of the group.

CASE 1.—A man aged 40 was injured on July 29, 1932, and was admitted to the hospital four hours later in coma. Examination revealed a laceration of the

scalp, hemorrhage from the canal of the right ear, cervical rigidity, bilaterally positive Babinski signs and a fracture of the skull in the right occiput.

Date	State of Patient	Initial Pressure, Mm.	Fluid Removed, Cc.	Appearance
7/30/32	Coma	400	55	Bloody
	After first puncture patient immediately became conscious and rational	450	90	Bloody
7/31/32	Conscious	225	60	Bloody
8/1/32	Conscious	200	55	Yellow

Coma and high spinal fluid pressure persisted for three days. After the withdrawal of 90 cc. of fluid consciousness returned; the patient became rational and was without complaints.

CASE 2.—A man aged 26 was injured on March 26, 1933, when his horse fell on him. He was unconscious for ten minutes and not entirely mentally clear until

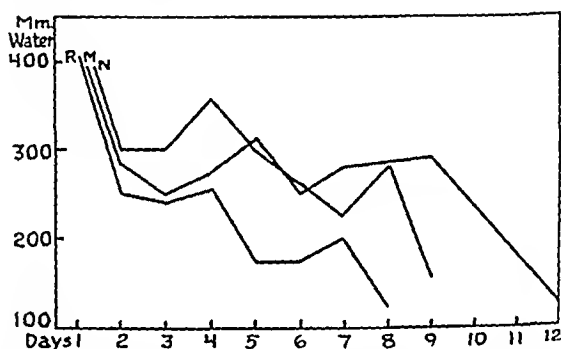


Chart 2.—Curves (designated by the initial of the patient) showing the progressive fall in the spinal fluid pressure of patients on whom drainage was done within the first or second day after injury. *M* indicates the curve for the patient in case 6, and *N* the curve for the patient in case 4.

after he was admitted to the hospital. Examination revealed ecchymosis of the lids of each eye, epistaxis and crepitus over the right antrum. The skull was fractured in the left occiput.

Date	State of Patient	Initial Pressure, Mm.	Fluid Removed, Cc.	Appearance
3/27/33	Patient was confused; complained of headache; severe headache disappeared 30 min. after spinal puncture; did not return for two days, although high spinal fluid pressure continued; conscious	350	30	Bloody
3/28/33	Conscious	325	30	Blood tinged
3/29/33	No complaints	200	16	Blood tinged
3/30/33		160	15	Blood tinged

The patient's confused mental state and severe headache, which had been present for twenty-four hours, were promptly relieved after the first spinal drainage. There were no complaints after the spinal fluid pressure remained below 200 mm.

CASE 3.—A Mexican boy aged 7 years was struck by an automobile on Jan. 11, 1933. The duration of coma was unknown. Examination on his admission to the hospital showed stupor, cervical rigidity, tortuous retinal veins and filling of the optic cups.

Date	State of Patient	Initial Pressure, Mm.	Fluid Removed, Cc.	Appearance
1/12/33	Stupor; vertigo			
1/13/33	Headache	320	14	Bloody
1/14/33	Less headache	370	15	7% blood
1/15/33	Still headache	220	14	4% blood
1/17/33	Felt better and wanted to go home	175	4	Slightly bloody

The headache was less after the second spinal drainage. The patient was much improved when the spinal fluid pressure was reduced to 175 mm. There was progressive clearing of blood from the cerebrospinal fluid.

CASE 4.—A boy aged 6 years was struck by an automobile on Jan. 22, 1933. Examination on his admission to the hospital showed a laceration of the scalp, cervical rigidity and a questionable positive Babinski sign on the left side.

Date	State of Patient	Initial Pressure, Mm.	Fluid Removed, Cc.	Appearance
1/23/33	Semistuporous	400	32	1% blood
1/24/33	Still semistuporous; tossed about	300	30	0.3% blood
1/25/33	Comatose	300	28	Trace of blood
1/26/33	A little better	360	35	Trace of blood
1/27/33		300	44	Trace of blood
1/28/33	A little brighter	260	23	Slightly bloody
1/30/33	More rational; less stuporous	230	18	Clear
1/31/33	Restless	260	25	Clear
2/ 1/33	Improving	160	15	Clear
2/ 4/33	"Fogged," but no headache and no complaints	200	22	Clear
3/ 7/33	Symptom-free			
6/ 6/33	Well; going to school			

The patient's improvement was progressive and uneventful, particularly when the pressure was reduced to 230 mm. Restlessness recurred when the pressure was 260 mm.; improvement occurred again when the pressure was 160 mm.

CASE 5.—A man aged 28 was injured in an automobile collision on May 8, 1932. He was unconscious for several hours. Examination showed a laceration of the

scalp, distention of the bladder and a slow pupillary reaction. A fracture of the right side of the front of the skull extended into the orbit.

Date	State of Patient	Initial	Fluid	Appearance
		Pressure, Mm.	Removed, Cc.	
5/ 9/32	Comatose	300	23	Moderately bloody
5/10/32	Vomited	300	16	Moderately bloody
5/11/32		250	25	Blood tinged
5/12/32	Incontinent	125	12	Slightly bloody
5/18/32	Very rational	140	15	Faintly yellow
5/22/32	Fully conscious			

Stupor persisted for five days. With a progressive fall in the pressure, there was return of consciousness when the pressure was reduced to normal.

CASE 6.—A man aged 32 was struck by a street car on Feb. 22, 1933. Examination on his admission to the hospital showed stupor, a laceration of the scalp, cervical pain and rigidity. The right eyelids were ecchymotic, and blood was present in the left aural canal. The Babinski and Chaddock signs were positive bilaterally. Fractures were present in the left parietal region and in the second cervical vertebra.

Date	State of Patient	Initial	Fluid	Appearance
		Pressure, Mm.	Removed, Cc.	
2/22/33		410	35	50% blood
2/22/33	Stuporous	300	30	0.01% blood
2/23/33	Irrational	250	25	Slightly red
2/24/33	Rational	275	25	Slightly red
2/25/33	Better	325	35	Bloody
2/26/33		250	5	Slightly bloody
2/27/33		270	25	Slightly yellow
2/28/33	Restless and noisy; temp. 103 F.; otitis media and mastoiditis	400	40	Clear
3/ 1/33	Improved; drowsy	270	40	Slightly yellow
3/ 2/33	Less restless	110	5	Light yellow
3/ 4/33		150	25	Light yellow
3/ 5/33	Rational			

The patient was stuporous and irrational, with a high spinal fluid pressure (410 mm.), until after the fourth puncture, when he became rational. He again became irrational and had a high pressure, when mastoiditis developed, and finally he became rational after the spinal fluid pressure was reduced to normal.

Subgroup 2: Drainage Delayed From Five to Eight Days.—There were nine patients in whom, although there was a progressive fall in pressure with corresponding clinical improvement, the treatment for some reason was delayed until after the fourth to the seventh day.

The outstanding feature in these patients was the persistence of pressure symptoms before drainage and the marked and almost spectacular immediate (subjective) improvement in symptoms after the first puncture. The only apparent difference in the pressure in this group as compared with that in the group of patients who were treated early was that in the latter the average pressure of the last puncture was 20 mm. lower. The severity and persistence of the symptoms in patients in whom drainage was delayed has convinced me that in most instances treatment is indicated as soon as the patient comes under observation.

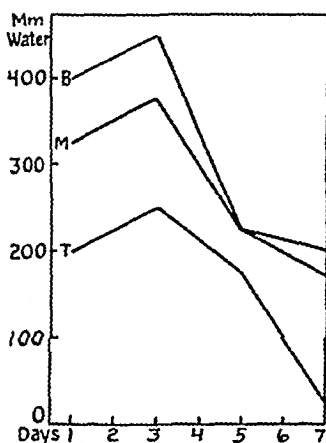


Chart 3.—Curves (designated by the initial of the patient) showing the progressive fall in the spinal fluid pressure of patients on whom drainage was done within the first or second day after injury. *B* indicates the curve for the patient in case 1, and *M*, the curve for the patient in case 3

The following cases (chart 4) illustrate this group:

CASE 7.—A man aged 27 was struck by an automobile on May 3, 1932. Coma lasted for thirty minutes. Examination showed laceration of the scalp, cervical rigidity and fracture of the skull in the left temporal bone

Date	State of Patient	Initial Pressure, Mm.	Fluid Removed, Cc.	Appearance
5/ 7/32	Severe headache			
5/ 8/32	Severe pain in the head	300	30	Very bloody
5/ 9/32	Improved but still much headache	300	25	Moderately bloody
5/11/32		200	15	Clear
5/13/32	No headache	200	2	Slightly yellow

Treatment was delayed for five days, thereafter an elevated spinal fluid pressure persisted. However, clinical improvement resulted after repeated drainage

CASE 8.—A boy aged 12 years fell from a car on Feb. 24, 1933, and was in coma for twenty-four hours. Severe headache followed. Examination showed ecchymosis of the left eye, bilaterally positive Babinski and Chaddock signs and a fracture in the left temporal bone extending into the middle cranial fossa.

Date	State of Patient	Initial	Fluid	Appearance
		Pressure, Mm.	Removed, Cc.	
3/ 2/33	Severe headache	340	36	Clear
3/ 3/33	"Much better since spinal puncture yesterday"	335	50	Clear
3/ 4/33	"Perfectly well now"	250	45	Slightly yellow
3/ 5/33	Very well; wanted to go home	400	50	Clear
3/ 6/33		310	25	Slightly yellow
3/ 7/33		215	40	Slightly yellow
3/ 9/33	Very well; wanted to go home	175	20	Slightly yellow
3/10/33	Very well; wanted to go home	215	25	Slightly yellow

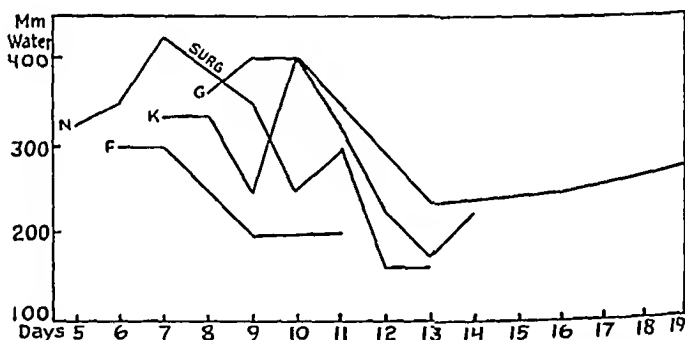


Chart 4.—Curves (designated by the initial of the patient) showing the progressive fall in the spinal fluid pressure of patients on whom drainage was delayed for five, six, seven and eight days. *F* indicates the curve for the patient in case 7; *K*, the curve for the patient in case 8, and *G*, the curve for the patient in case 9.

There were severe concussion with pathologic reflexes and fracture of the skull, severe headache and high pressure (340 mm.). Treatment was delayed for six days; symptoms were relieved immediately by drainage; however, the pressure remained high until after the fifth puncture.

This case illustrates the difficulty in reducing pressure when treatment is delayed. Relief from symptoms was obtained on drainage.

CASE 9.—A Mexican aged 25 was struck on the head on Jan. 10, 1933; the duration of coma was unknown. He was admitted to the hospital seven days later, complaining of severe headache. Examination revealed cervical rigidity, papilledema of 3 diopters, retention of urine and an Oppenheim reflex on the right.

A vertical occipital fracture was present. The headache immediately improved after the first spinal drainage.

Date	State of Patient	Initial	Fluid	Appearance
		Presence, Mm.	Removed, Cc.	
1/17/33	Pulse rate, 54 to 60	360	45	Slightly bloody
1/18/33	Better; pulse rate, 52 to 60;	400	40	Slightly bloody
	still some headache	400	50	Slightly bloody
1/21/33	Less headache but still groaned; pulse rate, 68 to 100	230	38	Trace of blood
1/24/33	Slept considerably	250	8	?
1/27/33	Ambulatory; slight headache	270	35	Clear
1/30/33	"Felt fine"			
1/31/33	Discharged			

There were concussion and fracture of the skull, high pressure and severe headache. Treatment was delayed for seven days; marked improvement occurred when the pressure reached 230 mm. It was difficult to get the pressure below 230 mm. (delayed treatment).

GROUP B: SUSTAINED PRESSURE

There were twelve patients in whom the pressure of the cerebrospinal fluid continued high (from 200 to 400 mm.) in spite of repeated spinal drainage. In some of these patients there was an abrupt drop to around 200 mm., but subsequent punctures again showed a high pressure. In general, pressure symptoms continued and did not improve until after several punctures had been done. In a few patients the headache disappeared early in the series of drainages, although the pressure continued at a high level. In every patient the headache was finally controlled if treatment was continued faithfully.

I can offer no satisfactory explanation for the sustained pressure in this group other than the possibility that there were actually more concussion and stimulation to the choroid plexuses, resulting in a greater output of cerebrospinal fluid with possibly loculated subdural fluid. Most patients presented a clinical picture which paralleled the high pressure, for in the group there were two deaths, and it was necessary to operate on four patients. This clinical correlation was not constant, however, for headache disappeared readily in two patients who continued to have elevated pressure (from 250 to 300 mm.).

This group of patients was subdivided into those whose treatment was instituted early and those whose treatment was delayed. Here again there was no difference clinically other than a failure of the symptoms to improve until spinal drainage was instituted.

The following cases are representative of the group.

CASE 10.—A man aged 31 was injured in an automobile accident on Jan. 28, 1933. He was in coma for one hour and stuporous thereafter. Examination revealed laceration of the scalp, cervical rigidity, absence of the right abdominal reflex and positive Babinski, Chaddock and Oppenheim signs bilaterally.

Date	State of Patient	Initial Pressure, Mm.	Fluid Removed, Cc.	Appearance.
1/30/33	Stupor; headache	200	25	1% blood
1/31/33	Stupor; pulse rate, 52	220	23	Slightly bloody
2/ 1/33	Conscious; some headache; pulse rate, 45	300	34	Yellow
2/ 2/33	Less headache; ate; pulse rate, 56	300	35	Yellow
2/ 3/33	Same, but less headache; pulse rate, 56	230	32	Slightly bloody
2/ 4/33	Headache continued; pulse rate, 72	300	28	Slightly bloody
2/ 5/33	Headache continued; pulse rate, 70	250	34	Slightly bloody
2/ 6/33	No headache; pulse rate, 76			
2/ 7/33	Up; felt well; pulse rate, 68	250	40	Clear
2/ 8/33	No complaints; pulse rate, 62	270	40	Clear
2/ 9/33	No complaints	250	42	Clear
2/10/33	Felt "like a million"	200	34	Clear
2/11/33	No complaints	210	34	Clear



Chart 5.—Curves (designated by the initial of the patient) showing the sustained high spinal fluid pressure in spite of repeated drainage. *B* indicates the curve for the patient in case 10. In this case the pressure was still elevated after the thirteenth puncture. Patient *G* died after surgical intervention (indicated by *x*).

Increased spinal pressure was sustained (from 200 to 300 mm.), but pressure symptoms definitely improved after the pressure was kept below 250 mm.

CASE 11.—A sailor aged 19 was thrown from a motorcycle on Sept. 18, 1931. He was admitted to the hospital in deep coma with stertorous respiration. Examination revealed laceration of the scalp, epistaxis and ecchymosis of each eye.

The neck was rigid anteroposteriorly, and the Babinski sign was positive bilaterally. The pulse rate was 68 and the temperature varied from 100 to 102 F. No fracture was shown roentgenographically.

Date	State of Patient	Initial Pressure, Mm.	Fluid Removed, Cc.	Appearance
9/19/31				
10 a. m.	Still in deep coma	400	45	Slightly bloody
9 p. m.		400	45	Slightly bloody
9/20/31				
10 a. m.	In deeper coma; temp., 103 F.	200	25	Slightly bloody
7 p. m.	Right hemiparesis	350	30	Slightly bloody
9/21/31	Operation: left subtemporal decompression; a large amount of subdural clot and blood-tinged fluid, with severe cortical contusion, subpial hemorrhage and increased intracerebral tension; drainage of subdural space	300	35	More bloody
9/22/31	Coma lighter; temp., 101.6 F.			
9/23/31	More restless; pulse rate, 70	280	25	Yellowish
9/24/31	Much improved; less stuporous			
9/26/31	Some improvement	380	45	Slightly bloody
9/28/31	Improved	400	70	Clear
9/29/31		380	45	Clear
10/ 2/31	Took fluid well	140	30	Clear
10/ 8/31		150	16	Clear
10/13/31	Conscious; motor aphasia	200	24	Clear

The patient suffered from severe concussion, cortical contusion and a basilar fracture. There were a high cerebrospinal fluid pressure and an excessive amount of spinal fluid with a localized subdural clot. The patient became worse on the third day despite drainage of the spinal fluid, the pressure remaining high. There was improvement after the surgical removal of the clot and drainage, but the pressure still remained high (from 280 to 400 mm.); the patient was stuporous for nine more days until the pressure became lower (from 140 to 150 mm.). He was conscious on the twenty-fifth day, when the pressure was found to be only 200 mm.

This is a case in which spinal drainage was insufficient, and continued failure indicated a surgical lesion. In addition, postoperative drainage of the spinal fluid was also indicated.

CASE 12.—A man aged 32 was in an automobile accident on Feb. 1, 1933. He was rendered unconscious, had convulsions and vomited once. Examination revealed cervical rigidity, ecchymosis of the left eye, laceration of the scalp, a

positive Babinski sign bilaterally and pathologically positive deep reflexes. No fracture was shown roentgenographically.

Date	State of Patient	Initial Pressure, Mm.	Fluid Removed, Cc.	Appearance.
2/ 1/33	Deep coma	200	20	11% blood
2/ 2/33	Semicomatose	250	26	4% blood
2/ 3/33	Could be aroused	300	32	Trace of blood
2/ 4/33	Talked loudly	320	32	Yellow
2/ 5/33	Condition the same	210	28	Slightly yellow
2/ 6/33	More rational	190	24	Clear
2/ 7/33	Quiet; no restraints	210	?	Clear
2/ 9/33	Entirely rational	250	?	Clear
2/11/33	Awake; remembered nothing since accident	190	?	Clear

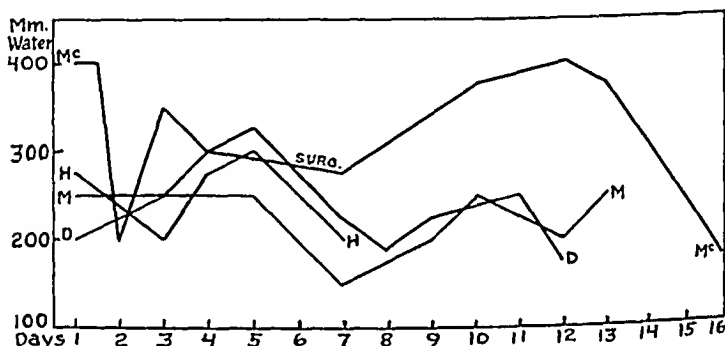


Chart 6.—Curves (designated by the initial of the patient) showing the sustained high spinal fluid pressure in spite of repeated drainage. *Mc* indicates the curve for the patient in case 11, and *D* the curve for the patient in case 12. In case 11 the pressure was still elevated until after the fourth postoperative puncture.

The patient was comatose and irrational for eight days. The spinal fluid pressure ranged from 200 to 320 mm. He became markedly better when the pressure reached 190, and did not relapse, even though the pressure rose again to 250 mm.

GROUP C: SECONDARY RISE AFTER "NO DRAINAGE INTERVAL"

The third group of patients, a most interesting one, presented a secondary rise in pressure (from 200 to 400 mm.) after an interval without treatment. This group best illustrates the necessity of continued observation and drainage at close intervals in order to keep cerebrospinal fluid pressure normal. There was not always a return of headache and stupor when the pressure would be found elevated after an interval of no drainage, but whenever symptoms did return, the pressure was always found high, and symptoms were relieved by drainage.

The period of no drainage varied from two to several days. It was found that an interval early in the course of treatment was more likely to result in a secondary rise of pressure than was a similar interval later in the course of observation. This should emphasize the necessity of an early and earnest attempt at reestablishing normal cerebrospinal fluid pressure.

The group was divided into (1) those patients whose pressure had been reduced from high (from 300 to 400 mm.) to nearly normal,

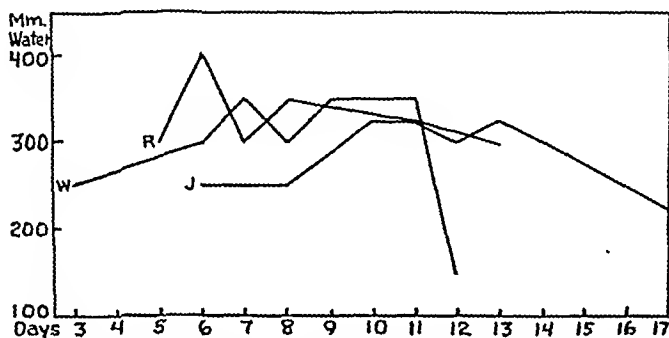


Chart 7.—Curves (designated by the initial of the patient) showing the sustained high spinal fluid pressure in spite of repeated drainage.

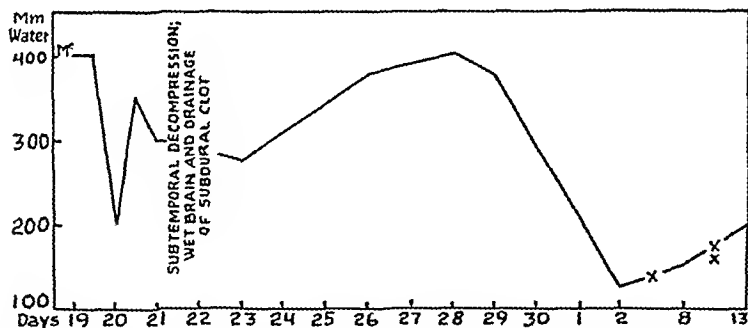


Chart 8.—Spinal fluid pressure curve for the patient in case 11. The pressure was sustained after operation until after the fourth puncture. The *x* indicates an interval of six days and *xx*, an interval of five days.

then after a "no drainage interval" was found to be high (charts 9 and 10) and (2) those whose pressure was at first nearly normal, but later after a "no drainage interval" secondarily rose to from 250 to 300 mm. (chart 11). For instance, a patient was injured on April 3, 1932. The pressure that day was 175 mm. No puncture was done again until April 6, when the pressure was 325 mm.; on

April 8 it was 325 mm. and on April 11, 350 mm. In the presence of continued stupor and headache after the first spinal puncture, drainage should have been repeated at least every twenty-four hours to insure against such secondary rise.

The cases reported here illustrate that observation should extend from two to three weeks in the presence of concussion in order to discover a secondary recurrence in symptoms and a rise in pressure.

Caution must be observed, however, in interpreting these recurrences, for instead of a simple reaccumulation of cerebrospinal fluid which could easily be controlled by drainage, one may be dealing with an (interval) extradural hematoma or a subacute subdural hematoma, in which case not only would surgical intervention be indicated but spinal punctures would actually be contraindicated. Only experience in close observation of clinical symptoms and interpretation of neurologic signs can differentiate these lesions. This question will be discussed later. However, case 13 will illustrate this point.

CASE 13.—A man aged 44 was drunk and fell on Nov. 23, 1931. On his admission to the hospital he was stuporous. A fracture was present in the left parietal region.

Date	State of Patient	Initial	Fluid	Appearance
		Pressure, Mm.	Removed, Cc.	
11/23/31		280	?	Blood tinged
11/24/31		150	8	Clear
11/27/31	Aphasic; restless	400	30	Clear
11/28/31	More stuporous	400	35	Clear
	Left hemiparesis	300	30	Clear
11/29/31	Operation: right subtemporal decompression; subdural and intracerebral hemorrhage; death twelve hours after operation			

In this case there was a delayed but marked increase in both generalized pressure and localizing signs which did not improve readily under drainage; these indicated a surgical lesion. Surgical intervention was delayed too long. Failure of the patient to improve within the first twelve hours after such a rise in pressure should indicate operation.

Another patient was injured on Sept. 29, 1932. Pressure on the second day was 125 mm.; on the sixth day, 450 mm.; on the seventh day, 450 mm.; on the eighth day, 350 mm., and finally, on the ninth day, 175 mm.

Subgroup 1: First Pressure High.—CASE 14.—A man aged 23 was thrown about 50 feet from a motorcycle on March 1, 1933. Examination on his admis-

sion to the hospital showed him to be in a confused mental state, with laceration of the scalp and cervical rigidity. A left parietal fracture was demonstrated roentgenographically.

Date	State of Patient	Initial	Fluid	Appearance
		Pressure, Mm.	Removed, Cc.	
3/ 1/33	Confused	490	15	10% blood
3/ 2/33	Severe headache and pain	100	3	0.2% blood
3/ 4/33	Relieved by spinal puncture	250	10	Bloody
3/ 4/33	Relieved by spinal puncture	400	20	Blood tinged
3/ 5/33	Patient stated that relief of headache after spinal puncture was immediate and lasted from 6 to 8 hours; complained of severe headache in morning and could not raise head from pillow			
3/ 5/33		400	20	Clear; yellow
3/ 6/33	Headache only slight	50	0	Clear; colorless

The first spinal fluid pressure was high; the second was low. No drainage was done on third day; on fourth and fifth days the pressures were again elevated.

CASE 15.—A man aged 27 fell from his horse on May 24, 1931. The neck was rigid; the Babinski sign was positive on the right.

Date	State of Patient	Initial	Fluid	Appearance
		Pressure, Mm.	Removed, Cc.	
5/25/31	Arousing; headache	300	40	Bloody
5/26/31	Irrational	130	15	Bloody
5/28/31	More rational	300	30	Blood tinged
5/29/31	Very stuporous			
5/31/31	Operation: right subtemporal decompression; large amount of clear yellow cerebrospinal fluid subdurally under pressure			

A secondary rise in pressure from 130 to 300 mm. occurred after an interval of one day. A large amount of fluid was found subdurally at operation.

CASE 16.—A boy aged 16 years was struck by an automobile on August 5, 1932, causing stupor, emesis and fracture in the left parietal region.

Date	State of Patient	Initial	Fluid	Appearance
		Pressure, Mm.	Removed, Cc.	
8/ 7/32	Stuporous	300	35	Bloody
8/ 8/32	Less stuporous	220	30	Clear
8/ 9/32		160	35	Bloody
8/14/32		300	25	Clear

There was a progressive fall of pressure from 300 to 160 mm. and then a secondary rise to 300 mm. after a "no drainage interval" of five days.

CASE 17.—A man aged 29 was in an automobile accident on May 8, 1932. Examination showed him to be in profound coma and involuntary, with a temperature of 104.6 F. There were abrasions of the face and scalp, ecchymosis of the left eye and small fixed pupils. The right clavicle and humerus were fractured.

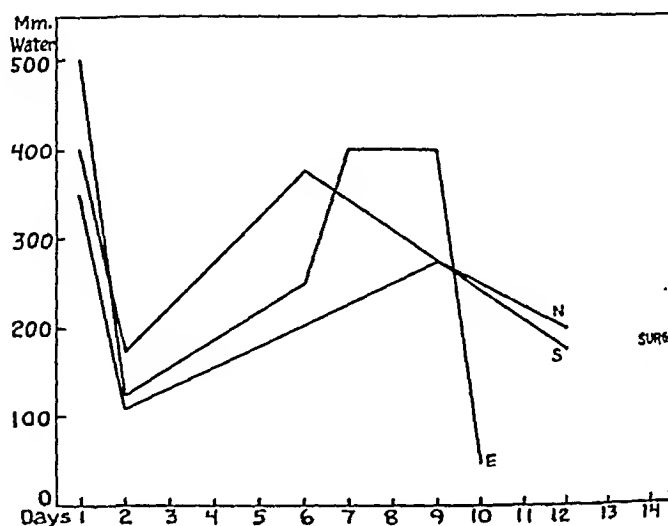


Chart 9.—Curves (designated by the initial of the patient) showing a secondary rise in spinal fluid pressure after a “no drainage interval” of from four to seven days. The first pressures were high. *E* indicates the curve for the patient in case 14.

Date	State of Patient	Initial Pressure, Mm.	Fluid Removed, Cc.	Appearance
5/10/32	Slightly improved	350	25	Moderately bloody
5/11/32	Coma	350	25	Moderately bloody
5/12/32	Coma	375	35	Blood tinged
5/13/32	Coma	275	15	Clear; colorless
5/14/32	Temp., 105 F.; bronchopneumonia	125	5	Clear; colorless
5/18/32	Coma			
5/21/32	Coma; improved			
5/26/32	Left pupil larger; Babinski sign bilaterally			
5/27/32	More conscious; aphasia	325	30	Clear; colorless
6/4/32	More conscious	280	20	Clear; colorless
6/8/32		180	15	Clear; colorless
6/20/32	Operation: left subtemporal decompression; brain contused and very wet; large amount of drainage for two days			
6/22/32	Looked better			
7/13/32	Asked for water			
7/26/32	Fed self	200	15	Clear; colorless

The patient suffered from concussion and contusion. The pressure was high but came down to 125 mm. on the fifth puncture. A later series of punctures brought the pressure from 325 to 180 mm. An operation, draining the subdural space of much fluid, gave definite improvement. Spinal puncture thirty-six days later gave a pressure of 200 mm. The patient asked for water on the sixty-third (posttraumatic) day. His mental state improved on the eightieth day. He was discharged on the ninetieth day, with a drawling speech, impairment of hearing and a Babinski sign on the right. Two months later he could walk, but with a spastic gait.

This patient was adequately treated by spinal drainage, but surgical drainage was necessary to drain the subdural space. This might better have been done earlier.

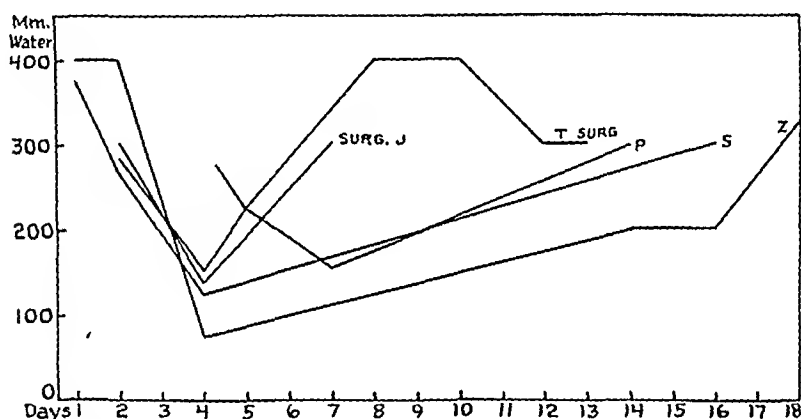


Chart 10.—Curves (designated by the initial of the patient) showing a secondary rise in spinal fluid pressure after a "no drainage interval" of from one to seven days. The first pressures were high. *J* indicates the curve for the patient in case 15; *T*, the curve for the patient in case 13; *P*, the curve for the patient in case 16, and *S*, the curve for the patient in case 17.

Subgroup 2: First Pressure Low.—CASE 18.—A man aged 46 was struck by an automobile on April 3, 1932. Examination on his admission to the hospital showed him to be irrational. The pupils were unequal, and the neck was rigid. The skull was fractured in the right temporal and left occipital regions.

Date	State of Patient	Initial Pressure, Mm.	Fluid Removed, Cc.	Appearance
4/ 3/32	Semicomatose	175	15	Very bloody
4/ 6/32	Still drowsy	325	15	Moderately bloody
4/ 8/32		325	18	Bloody
4/11/32		350	20	Blood tinged

The spinal fluid pressure at first was relatively low (175 mm.), but was found to be elevated (325 mm.) after a "no drainage interval" of two days.

CASE 19.—A man aged 39 was struck on the head with a chair on May 14, 1932. He was dazed, but not unconscious. Examination revealed laceration of the scalp, cervical rigidity and a fracture of the skull in the left parietal area. He complained of severe headache.

Date	State of Patient	Initial	Fluid	Appearance
		Pressure, Mm.	Removed, Cc.	
5/18/32	Severe headache	150	5	"Almost pure blood"
5/20/32	Severe headache	350	30	Very bloody
5/23/32	Severe headache	218	30	Clear; yellow
5/24/32	Headache better			
5/25/32		175	15	Slightly yellow

The first pressure was normal, but two days later it was elevated to 350 mm.

CASE 20.—A Mexican aged 32 was unconscious for thirty minutes after an automobile accident on April 24, 1932. Examination showed cervical rigidity, bleeding from the right ear, ecchymosis of the left eye and a double linear fracture of the skull in the right occiput.

Date	State of Patient	Initial	Fluid	Appearance
		Pressure, Mm.	Removed, Cc.	
4/27/32	Headache and vomiting	175	8	Moderately bloody
5/ 2/32	Temp., 103 F.; mastoiditis	300	20	Clear
5/ 4/32	Temp., 105 F.; mastoidectomy	300	16	?

After a "no drainage interval" of five days the pressure had increased from 175 to 300 mm.

CASE 21.—A Mexican youth aged 18 was in an automobile accident on Sept. 29, 1932, and sustained injuries of the back and head. Examination showed cervical rigidity and tenderness, paresis of the right arm and leg and a positive Babinski sign bilaterally. A fracture was present in the right parietal area.

Date	State of Patient	Initial	Fluid	Appearance
		Pressure, Mm.	Removed, Cc.	
9/30/32	Coma	125	3	Bloody
10/ 4/32	Coma	450	16	Bloody
10/ 5/32	Coma	450	12	Blood tinged
10/ 6/32	More conscious	350	11	Yellow
10/ 7/32	More conscious	175	8	Yellow
10/ 8/32		15	0	
10/14/32	More rational			

The spinal fluid pressure increased from 125 to 450 mm. after a "no drainage interval" of four days, returning to normal on repeated drainage.

SURGICAL DRAINAGE

The question of surgical intervention in cases of head injury is an important and difficult one. A large experience in clinical observation

and interpretation of the clinical course and neurologic signs is indispensable in determining the time and type of intervention. It goes without saying that a knowledge of the physiologic and pathologic pictures of intracranial pressure is most essential.

This series of patients afforded an excellent opportunity to study the preoperative and the postoperative clinical course as compared with the spinal fluid pressure findings and to check both of these with surgical and postmortem observations.

INDICATIONS

The indications for surgical intervention depend entirely on a diagnosis. All that one can expect to accomplish by surgical measures is to remove or drain a lesion which is causing pressure. Of these lesions,

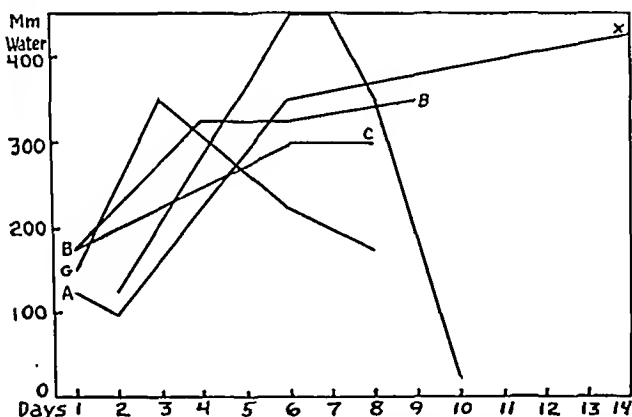


Chart 11.—Curves (designated by the initial of the patient) showing a secondary rise in spinal fluid pressure after a “no drainage interval” of from one to three days. The first pressures were low. *B* indicates the curve for the patient in case 18; *G*, the curve for the patient in case 19, and *C*, the curve for the patient in case 20. *X* indicates the finding of choked disks. Operation performed fifty-four days later showed excessive subdural and subarachnoid fluid.

there are only three: (1) extradural hematoma, (2) subdural hematoma and (3) a subdural (extra-arachnoid) accumulation of fluid.

The third lesion is by far the most commonly neglected one. It consists of cerebrospinal fluid which is loculated subdurally, either by seepage through the arachnoid due to increased subarachnoid pressure or to arachnoidal tears. This lesion was present in ten of the fourteen cases in this series in which operation was performed. It is immediately recognized as a “gush” of yellow or pink fluid when the dura is opened. It is easily removed by a trephine sufficiently large to admit a surge-

line drain. The drainage is profuse for from twelve to thirty-six hours, after which it usually ceases.

Subdural accumulation of fluid is by far the most common operative lesion and no doubt the least recognized. Differentiation from a subdural hematoma is not easy. Its presence may well be suspected when, after the third or fourth day, in spite of repeated spinal drainage, stupor, coma and headache fail to improve. In addition, a most valuable and almost unfailing accompanying finding is the persistence of high cerebrospinal fluid pressure (charts 5, 6 and 7).

The presence of cortical contusions may materially distort the picture and cause considerable difficulty in diagnosis. To the inexperienced surgeon, hemiparesis resulting from contusions may tend to urge him to explore. The outstanding feature of contusion causing paresis and reflex changes is the presence of these findings almost immediately after injury, particularly if associated with clear or improving consciousness. There may or may not be high cerebrospinal fluid pressure. Such localizing findings which had been present from the first in a patient who is slowly, over a period of days, becoming more stuporous, suggests contusions plus subdural hematoma or subdural accumulation of fluid. Even when complicated by either of the latter two lesions, the presence of paresis from the moment of injury is still indicative of cortical contusion or laceration.

LESIONS FOUND AT OPERATION

Before discussing the clinical aspect of cases in which operation was performed, it will be of value to give an idea of the surgical lesions actually found at operation in fourteen cases.

The most common lesion was the typical "wet brain" caused by subdural and subarachnoid collections of fluid. This was present in ten cases. Extradural hematoma was found once, subdural hematoma three times, intracerebral hemorrhage once and finally only a red, swollen brain twice. One of these was very dry; the other had some fluid, but the exact description was not recorded. The brief case reports which follow will give the type of lesion and the corresponding picture produced by spinal fluid pressure.

CLINICAL COURSE

Course.—In general, all patients became worse preoperatively and improved postoperatively. There were two deaths immediately after operation, one from intracerebral hemorrhage and one from cardio-renal and coronary disease. The third death occurred fifteen days post-

operatively from pneumonia. The state of the patient before operation and the result afterward are recorded in the following tabulation:

Symptom Before Operation	No. of Cases	Results After Operation	No. of Cases
Headache	4	Improvement	4
Coma	10	Revival	7
Hemiparesis	10	Improvement	8
Choked disks.....	2	Recession	2
Aphasia	5	Improvement	4
Spinal pressure sustained or increasing	12	Sustained or declined	8
Reflex changes.....	12	No record	
Pupillary inequality.....	6	No record	

All patients had a high spinal fluid pressure at some time before operation, and nine had a pressure over 250 mm. immediately before operation (charts 12 to 15).

There were three exceptions. The patient in case 22, after two punctures, had a preoperative pressure of 175 mm. At operation the brain showed considerable pressure and fluid subdurally. At postmortem examination (death fifteen days after operation due to pneumonia) there was no gross cerebral lesion, showing that spinal puncture and operation had removed the fluid by drainage. The other patient had had ten spinal punctures preoperatively, the last pressure being only 175 mm.; only a dry red brain was found at operation. Postmortem examination showed diffuse basilar subdural clots with laceration of the left temporal lobe, but no evidence of pressure on the brain! The patient in case 23 had a preoperative pressure of 175 mm., four spinal punctures having been done. There were redness and laceration of the cortex and considerable subdural clot, but no excess fluid.

The preoperative pressure of these three patients was relatively low (175 mm.). The first patient had only two spinal punctures, and much fluid remained. The second and third patients had ten and four spinal punctures, and the brains at autopsy (although having some subdural clots) showed little excess fluid and little evidence of cerebral compression.

There was often a tendency to be hurried into operation by the presence of hemiparesis, aphasia or both, even when the patient's consciousness and other signs of pressure showed improvement. The patient in case 23 was conscious and rational and had a normal spinal fluid pressure. There may have been some question regarding the necessity of removing a small amount of subdural clot to prevent later convulsions, but the course was favorable, and as there were no signs of pressure, surgical intervention was not indicated. Signs of deepening coma and increasing spinal pressure should cause much more concern than localizing signs. The latter are usually caused by contusions and

lacerations (not operable), while the former result from excess fluid or clots. In order for surgical measures to accomplish anything, there must be removal or drainage to provide more space. Since contusions and lacerations require little more space than normal brain, a definite differential diagnosis is necessary when considering operation.

Pupillary inequality should attract considerable attention in making a diagnosis of a surgical lesion, for in the comatose patient this sign is often the earliest and the most reliable sign localizing a pressure-producing lesion. Almost invariably one will find that when the patient is still conscious or lightly stuporous (stage of cerebral irritation) the pupil will be smaller on the side of the lesion. However, and this is more important, when the patient is moderately or deeply comatose, the lesion will be found on the side of the larger pupil. This sign was present in six cases and in every case indicated the side of the lesion. I have seen this sign fail but once, and that time it was thought that the patient had an additional lesion of the third nerve on the side opposite the hemorrhage.

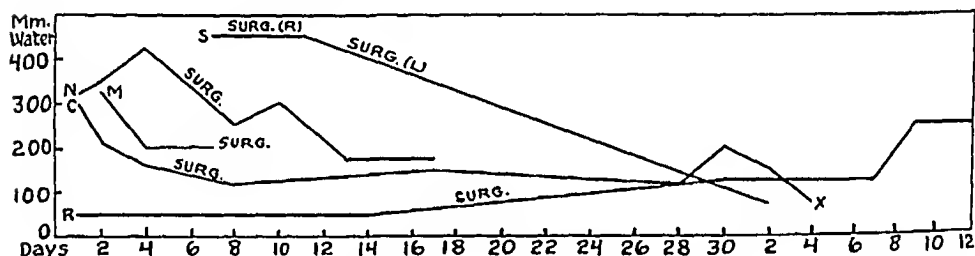


Chart 12.—Curves (designated by the initial of the patient) showing lowered spinal fluid pressure after surgical drainage. *S* indicates the curve for the patient in case 24; *M*, the curve for the patient in case 26; *C*, the curve for the patient in case 22, and *R*, the curve for the patient in case 29. All the patients recovered with the exception of one, who died of pneumonia (indicated by *x*).

CASE 13.—A man, aged 44, suffering from syphilis and addicted to the use of alcohol, sustained concussion and coma. On the sixth day spastic paresis developed on the left side, and the coma deepened. The spinal pressures were 280, 150, 400 and 300 mm. Signs of early medullary failure and hyperthermia developed. Operation showed subdural and intracerebral hemorrhage. Death occurred. In this case the spinal pressures paralleled the degree of coma and the localizing signs.

CASE 23.—The patient was in coma for four days after an injury and then awakened but was aphasic. Spinal punctures showed pressures of 400, 175, 375 and 175 mm. Operation revealed the dura to be tight and blue and the cortex lacerated and red, with some subdural hematoma. The patient was doing well before the operation. The spinal pressure had returned to normal or at least was being controlled by spinal drainage. Operation did not accomplish anything. The aphasia should not have been an indication for intervention.

CASE 24.—The patient was admitted to the hospital after five days of headache resulting from a blow on the head. The spinal pressure was 450 mm. Subtemporal decompression showed a swollen, red, contused cortex. No record was made of the amount of fluid, but a drain was inserted. Spinal pressure the next day was again 450 mm., so on the second day subtemporal decompression was done on the opposite side. Again no record was made of the findings, but the wound was drained, and the patient was remarkably improved and free from symptoms four days after the second operation. The patient's treatment was delayed for five days, but it is my opinion that he would have recovered as well by repeated spinal drainage.

CASE 25.—In this patient the preoperative spinal fluid pressure was 175 mm. Surgical exploration revealed a red, dry cortex not under increased tension. There was no excessive amount of fluid. The relatively low spinal fluid pressure should have indicated that there was little probability of an operable lesion.

There was one case in which an extradural hematoma was present and four cases in which there were subdural collections of fluid, which

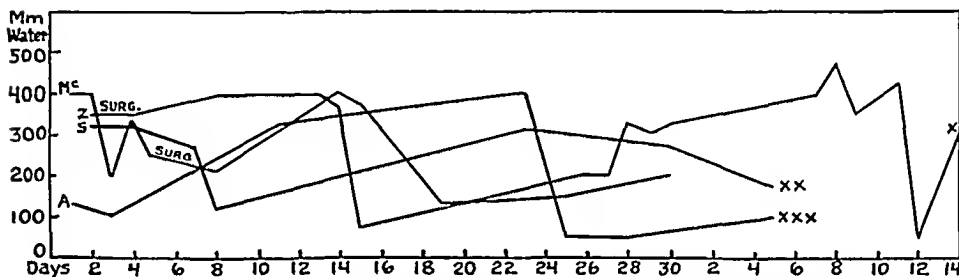


Chart 13.—Curves (designated by the initial of the patient) showing variations in the spinal fluid pressure (in two cases before operation and in two cases afterward). Often a much lower pressure was found the day after drainage. *Mc* indicates the curve for the patient in case 11; *S*, the curve for the patient in case 17; *A*, the curve for the patient in case 28, and *Z*, the curve for the patient in case 31. Patient *Z* woke fourteen days after the time indicated by *x*; patient *A* had a pressure of 400 mm. forty-four days after the time designated by *xxx*, and operation was performed seventy-eight days later; patient *S* was operated on twelve days after the time designated by *xx*, and the spinal fluid pressure was 200 mm. forty-eight days later.

will be described later under postoperative spinal drainage. Four additional cases in which there was excessive subdural fluid will be presented to emphasize the preoperative clinical course and the spinal fluid pressure.

CASE 26.—The patient's coma became deeper on the third day, and paresis developed on the left side. Spinal punctures showed pressures of 315, 200 and 200 mm., but the patient did not arouse after drainage. Operation performed on the fourth day revealed an excessive amount of fluid subdurally and a swollen cortex. There was much drainage postoperatively. The patient began to arouse on the sixth postoperative day, became rational on the ninth day and began to move the left side on the twentieth day; therefore no postoperative spinal drainage

was done. The sustained spinal fluid pressure and deepening coma with hemiparesis indicated operation for the drainage of subdural fluid which could not be adequately drained by the spinal route.

CASE 15.—The patient became more stuporous on the sixth day after injury, with a slow pulse, weakness of the left side of the face and spinal pressures of 300, 130 and 300 mm. Operation revealed a large amount of clear yellow fluid subdurally which continued to ooze through the arachnoid. The patient became more rational on the eleventh day but was not conscious until the eighteenth day. Three months later he stated that he was physically perfect and without headache but had deafness and tinnitus in the left ear. He also had a "wet brain" which could not be successfully managed by spinal drainage; however, postoperative drainages would probably have hastened the recovery of consciousness.

CASE 27.—The patient was in coma for four hours and was doing well except for increasingly severe headache, weakness on the right side and a larger pupil on the right than on the left. Spinal fluid pressures of 195, 180, 450, 230 and 240 mm. were obtained. Operation revealed a greenish blue dura, with a moderate amount of blood-tinged fluid beneath. The cortex was badly contused. Spinal fluid pressure on the third postoperative day was 280 mm. The drainage of 18 cc. of fluid relieved all symptoms, and the patient was still free from symptoms the next day.

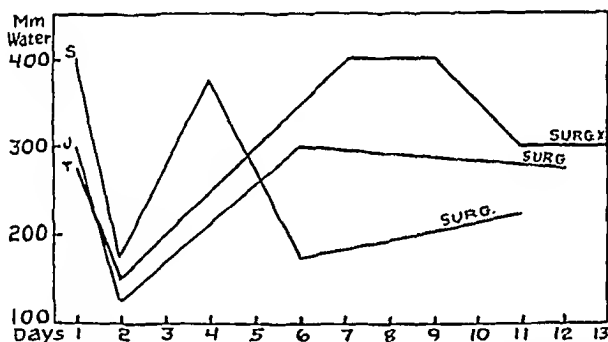


Chart 14.—Curves (designated by the initial of the patient) showing a low spinal fluid pressure the day after drainage, then a secondary rise followed by surgical drainage. *S* indicates the curve for the patient in case 23; *J*, the curve for the patient in case 15 and *T*, the curve for the patient in case 13. Death occurred in case 13 (indicated by *x*) due to intracerebral hemorrhage.

CASE 28.—This was a most interesting case. The patient was in coma for seventeen days with paresis on the right side, followed by aphasia. Later he contracted pneumonia, then otitis media and pain in the region of the mastoid. His speech returned by the twenty-eighth day. Spinal pressures of 130, 100, 350 and 400 mm. were obtained; then after drainage of from 10 to 30 cc. at a time the pressures were 50, 50 and 100 mm. There was no headache and no other complaints when on the seventy-first day, during an examination preceding discharge, choked disks were found and the spinal pressure was discovered to be 400 mm. Choked disks were still present two months later, whereupon a subtemporal decompression was done on the left side, revealing a tremendous amount of subdural yellow fluid. The brain receded from the skull after drainage of the fluid. Eight months later the disks appeared to be practically normal, and the boy was working hard without symptoms.

This case illustrates most forcibly the fact that some patients, particularly children, do not suffer from headache when they have increased intracranial pressure, even though the pressure is high enough to measure 400 mm. on the manometer and produce choked disks of 5 diopters, and that if there is the least indication of increased pressure after head injury, a puncture should be done to check the pressure and drain the excess fluid.

CASE 17.—The patient was in profound coma with a temperature of 104 F. immediately after injury. Pressures of 350, 350, 375, 275 and 125 mm. were obtained on successive days. Another series of punctures, begun fourteen days later and about four days apart, showed pressures of 325, 280 and 180 mm. The patient was still in coma after forty-three days; the left pupil was larger than the right, and the disks were blurred. Decompression in the left subtemporal region showed cortical contusion and an excessive amount of fluid; there was copious drainage of fluid for one or two days. On the sixty-third day the patient could ask for water and looked more intelligent. By the eightieth day there had been a

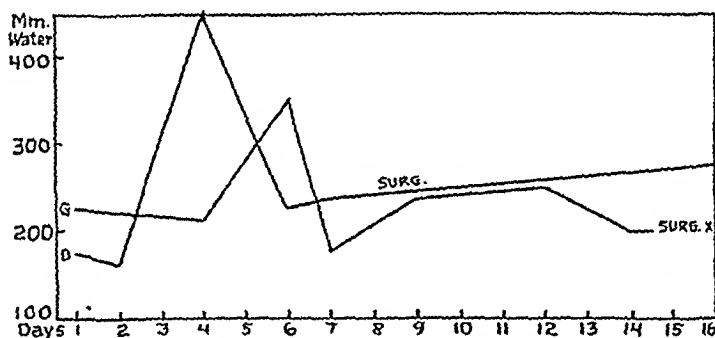


Chart 15.—Curves (designated by the initial of the patient) showing the spinal fluid pressure in cases in which surgical drainage was done. G indicates the curve for the patient in case 25, in which death occurred (x), due to cardiorenal disease; and D, the curve for the patient in case 27.

remarkable improvement in his mental status. On his discharge on the ninetieth day he had a drawling speech and some impairment of hearing. Two months later he had a spastic gait and slurring speech.

Postoperative Course.—There were three postoperative deaths, one from intracerebral hemorrhage, one from coronary disease and one from pneumonia.

All patients (four) conscious enough to complain of headache before operation were relieved of the headache postoperatively. Consciousness, however, was not quick to return; patients revived on the ninth, ninth, eleventh, twelfth, sixteenth, thirty-sixth and fifty-second day after operation. The patient usually regained consciousness slowly, although one patient (case 31) remained in coma for fifty-two days, then suddenly awakened. Another patient (case 17) gradually regained consciousness after thirty-six days. Hemiparesis was also slow to improve,

the patient never suddenly regaining use of the affected side. One patient (case 29) continued to have spasticity for several weeks. Aphasia disappeared by the time of discharge in four patients, but the fifth patient was still aphasic on leaving the hospital on the thirtieth day after injury. In one patient the disks returned to normal soon after surgical drainage of the cerebrospinal fluid. In the other the disks were normal eight months after operation.

No postoperative spinal punctures were done on four patients (owing either to freedom from symptoms on the part of the patient or to the fact that at that time the value of postoperative drainage was not realized). One puncture was done on each of two patients, one six days later, when the pressure was 280 mm., and the other forty-eight days later, when the pressure was found to be 200 mm. Two spinal punctures were done on one patient, the pressures being 400 and 60 mm. Four or more spinal punctures were done on five patients. The last group show particularly well the value of postoperative spinal drainage. A brief history of each case will be given.

CASE 29.—This case was unusual in that despite normal cerebrospinal fluid the clinical course was downward and localizing signs became more pronounced. After operation there was profuse subdural drainage for two days. However, on the fifth postoperative day the pressure was 180 mm. The patient remained in coma and in about the same general condition. On the fourteenth postoperative day the pressure was again found to be 180 mm., and 28 cc. of fluid was withdrawn. The next day the patient became conscious. I am unable to explain the low pressure before operation. It was possibly due to an error in technic. It was clear that the patient did not do well postoperatively until repeated spinal punctures were done and the increased pressure reduced by withdrawal of from 28 to 40 cc. per day.

CASE 30.—Preoperatively the patient had severe headache, vertigo and delirium at times. Spinal fluid pressures were 315, 350 and 435 mm., the fluid showing 0.35 per cent and 0.05 per cent of blood and at another time being "deep yellow." After operation the patient continued to be irrational and stuporous, with considerable headache. There was much subdural drainage for one or two days. The wound later became infected, but no more cerebrospinal fluid drained. Spinal fluid pressures continued to range from 250 to 350 mm. for three days, then the pressure was 160 mm., when the patient became much less confused, and by the eleventh postoperative day, during which time five punctures were done, withdrawing 36, 18, 30, 20 and 40 cc. of fluid, the patient became entirely conscious. The fluid correspondingly became bright yellow and then clear. The pulse preoperatively was in the sixties and occasionally seventies. Postoperatively, it was from 74 to 114, most of the time in the eighties and nineties, and never in the sixties.

This is an excellent example of continued postoperative coma and high pressure, both of which were improved by spinal drainage.

CASE 22.—Preoperatively, although the spinal pressure was approaching normal from 300 to 175 mm., the patient's coma deepened, and it was thought that there

must be some operable lesion. At operation a large amount of yellow fluid was found subdurally under markedly increased pressure. The brain collapsed as this was drained. Postoperatively the pressure was as high as 200 mm., and it was necessary to withdraw from 20 to 45 cc. of fluid on six successive punctures before the pressure remained normal. The patient died later of pneumonia; at postmortem examination the brain showed no gross lesion and no excessive amount of subdural fluid.

CASE 11.—Preoperatively there was deepening coma and right hemiparesis on the third day despite four spinal punctures in two days and another on the third day, pressures of 400, 400, 200, 350 and 300 mm. being obtained with the withdrawal of 45, 45, 25, 30 and 35 cc. of fluid. At operation a large amount of subdural clot and blood-tinged fluid was found under increased pressure; there were also severe cortical contusions and subpial hemorrhage. Postoperatively the pressure continued to range from 280 to 400 mm. for six days with drainage of from 25 to 70 cc. of fluid. Coma continued until after the pressure became 140 and 150 mm., when the patient became more rational.

This is an excellent case to illustrate that although spinal punctures were not sufficient preoperatively, neither was operation alone sufficient. It was only after further repeated spinal punctures, bringing the pressure to normal, that the patient began to arouse.

CASE 31.—This case is a most excellent example of the efficiency of postoperative spinal drainage. Preoperatively there was deep coma. The pressure was 400 mm., and the fluid was very red with blood. Hemiparesis and anisocoria developed on the third day. At operation an extradural hematoma was found, and in addition an excess of free fluid subdurally, cortical contusion and intracortical hemorrhage. Postoperatively the coma was less profound but continued for fifty-two days; then within two days the patient suddenly improved and awakened completely, was entirely rational and symptomless and told of a dream he had had of being confined in a straight-jacket and for many days cruising over Siberia. Spinal fluid pressures were 400 mm. on the third postoperative day and 400 mm. on the sixth and seventh postoperative days. At these times 60, 55 and 50 cc. of fluid were drained, and on the eighth day pressure was only 75 mm.! After a "no drainage interval" of ten days the pressures were 200, 200, 325, 300 and 325 mm. on successive days, and the decompression area still bulged. After another "no drainage interval" of six days, successive pressures were 400, 400, 350, 400 50 and 300 mm. The amounts drained varied from 30 to 52 cc. Further evidence of continued postoperative pressure was the bulging decompression area. The fluid at first was very bloody, but became and remained clear after the fifth puncture. In this case inevitable death from extradural hemorrhage was prevented by operation; however, cerebral "edema" continued throughout the period of coma, at times returning to normal on successive punctures, but with marked "secondary rises" after "no drainage intervals." It is questionable if the patient would have survived the long-continued cerebral compression from excessive cerebrospinal fluid had not repeated drainages been done. Another feature was that there was apparent freedom from mental impairment after fifty-two days of coma and periods of high intracranial pressure.

SUMMARY

1. By far the most common lesion found at operation was a subdural and subarachnoid accumulation of fluid.

2. In most cases spinal drainage controlled the symptoms and signs of pressure. In a few others the patient responded well to surgical (subtemporal) drainage.

3. Preoperatively, the degree of pressure symptoms and consciousness were closely paralleled by the spinal fluid pressure.

4. Postoperatively, continued coma and pressure signs were present in the majority of cases. These were markedly improved when intracranial pressure was controlled by further repeated spinal fluid drainage.

CONCLUSIONS

1. Continued observation and accurate diagnosis of the intracranial lesion are absolutely essential in preoperative care and for determining when surgical intervention is indicated.

In addition to shock and medullary failure, spinal puncture is contraindicated in extradural hematoma; therefore, accurate diagnosis is the prerequisite to all treatment.

2. Spinal puncture with pressure readings and drainage is a valuable and indispensable adjunct to operation both preoperatively, for decompression and for determining the progress of increasing or decreasing intracranial pressure, and postoperatively, for decompression by repeated drainage.

GENERAL CONCLUSIONS

I have not described a control group of patients not having drainage of cerebrospinal fluid with which to compare the patients here presented. I cannot be positive that repeated drainage does not after a time predispose to increased secretion of cerebrospinal fluid and thus tend to sustain increased pressure. However, under this treatment I have found: (1) frequent and immediate improvement in clinical signs, (2) a corresponding fall in pressure and improvement in clinical signs and symptoms, (3) secondary rises in pressure with recurrence of symptoms after "no drainage intervals," (4) sustained pressure and symptoms after a delay in treatment and (5) a shortened postoperative course by postoperative spinal drainage.

The foregoing clinical facts all point to the therapeutic value of spinal drainage in a large percentage of cases of increased intracranial pressure after concussion of the brain.

A further word is here appended. Too frequently the surgeon is interested only in the patient with a severe injury to the head or in the patient whose injury will necessitate operation. I appeal for an equally keen interest in the patient who sustains only minor concussion, perhaps not even causing loss of consciousness, for in this type of injury, too, much can be done in controlling intracranial pressure.

BIOMECHANICAL STUDIES OF FIBROUS TISSUES APPLIED TO FASCIAL SURGERY

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The purpose of this thesis is to present the results of determinations of the tensile strength, elasticity and proportional limit of selected fibrous mammalian tissues and to apply the findings to the solution of clinical problems. These determinations were made by utilizing engineering methods, and the results are graphically portrayed with a tabulation of any variation. A representative cross-section of adult mammals were studied, including rabbits, sheep, goats, dogs and man. Similar studies were also made on the young of the same species, and variations in the findings were contrasted with those noted in the study of adults of the same species, but these are not included in the present report. From each species representative fibrous tissues, particularly tendons and fasciae, were studied. In making the latter selection, tissues were chosen that were commonly used in transplantation and also that were involved in the syndrome of pain low in the back.

Adaptations of engineering methods permitted the graphic portrayal of the three physical properties selected. It was discovered that the fibrous tissues of mammals possess physical properties that are comparatively similar. This made the findings of this research and also many other researches conducted on animals pertinent to man. Determinations for normal adults were established (fig. 4), and the variations in all tests from these normal findings were graphically portrayed (fig. 3). The biomechanical tests and histologic studies which

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Presented as a thesis to the American Orthopedic Association in 1934. Presented in part before (1) the Society of Plastic and Reconstructive Surgery in Atlantic City, N. J., June 1935; (2) the New York Academy of Medicine, Section of Orthopedic Surgery, and the Philadelphia Orthopedic Club at a joint meeting at the New York Academy of Medicine in November 1935, and (3) the American Society for the Study of Arthritis in New York, December 1936. Portions of the material were also shown as a scientific exhibit before (1) the American Congress of Physical Therapy in September 1935 and September 1936, (2) the Medical Society of the State of New York in April 1936, (3) the American Medical Association in May 1936 and (4) the Graduate Fortnight on Trauma at the New York Academy of Medicine in October 1936.

have been completed show that the physical properties of tendons and those of fasciae are comparatively similar, thus making the research and clinical work on surgical procedures on tendons at least partially applicable to those on fasciae.

Variations from normal determinations due to shear phenomena and trauma were studied and the variations graphically portrayed (fig. 9). Shear and trauma were regarded as being the underlying causes of many of the unsatisfactory results in operations on fasciae, particularly in the transplantation of fibrous tissues. Variations in placing prepared sutures and in removing, handling and placing living sutures introduce shearing stresses, with resulting damage to the fibrous tissues repaired.

The rôle of trauma and shear in pain low in the back is also briefly presented not only in relation to the fibers themselves but in relation to the mesothelium covering of the fibers. The mesothelial cells covering the fibers are in intimate contact with the nerves and blood vessels traversing the fascial spaces. It is believed that radicular pain following a definite nerve distribution, such as sciatica, may in certain cases be caused by disturbed functions of the mesothelial cells, with resulting impingement on the nerves in locomotion.

The clinical value of these determinations in operations involving fasciae will depend primarily on the knowledge of the normal and deranged functions of the fascial planes. The methods and technic now used may be supplemented rather than replaced by the clinical application of these data.

SELECTION OF TISSUES AND ANIMALS FOR STUDY

While fibrous tissue in greater or less degree is found in all organs, it predominates in certain locations. Where support is the chief function, fascia develops; where special adaptations of form become necessary for the transmission of power from the muscles to their respective insertions in other portions of the locomotor apparatus, tendons and ligaments are found. Representative structures of these groups were studied biomechanically. The data obtained should simplify the study of fibrous tissues in other locations. The anatomic studies of fascia by Gallaudet¹ and Davies² deserve particular mention.

The fascial planes vary in thickness according to their location and function and invest the higher structures, i. e., muscles, cords, tendons, bursae, vessels, nerves, viscera and joints and even cartilage and bone.

1. Gallaudet, B. B.: *A Description of the Planes of Fascia of the Human Body*, New York, Columbia University Press, 1931.

2. Davies, J. W.: *Abdominal and Pelvic Fasciae with Surgical Applications*, Surg., Gynec. & Obst. **54**:495-504, 1932.

There are two principal planes of fascia: the subserous and the subcutaneous. Since fascia is subjected to varying factors of stress, its final adult form has probably been determined by functional variations. Fascia lata was selected for the study of the fascial planes because of its importance in pain low in the back and because of its extensive use in the transplantation of living sutures.

The function of fascia lata is muscular support as well as the transmission of varying directional stresses in the thigh, and it conforms histologically to these functions, being a composite of fibers arranged in varying planes.

In the second group of fibrous connective tissues the tendons seemed the logical choice. Their prime function is the transmission of power developed in the muscles to their osseous insertions. The tendo Achillis would be expected to show adaptations of form corresponding to the simplicity of its action.

Other tendons have a more complicated function. The flexor digitorum longus transmits power around one joint to multiple osseous insertions. As the function is necessarily more complex, it would be expected that its structure is more complicated than that of the tendo Achillis.

The fourth tissue studied, the erector spinae, has a supportive rather than a kinetic function and is of prime importance in pain low in the back. Work on these four structures comprise test data presented on experimental animals, which were the rabbit, dog, sheep and goat. The weight range of these animals was from 1.8 to 58 Kg.

Work was also done on the human patellar ligament, which has a direct attachment between two bones, and on the quadriceps tendon, the attachment of which is between its muscle through a sesamoid bone to the tibia. Among other tissues studied were the aponeurosis of the external oblique muscle and the central tendon of the diaphragm.

NOTES ON HUMAN TISSUE

The preliminary report was based on test pieces removed from patients at the time of operation.³ Since it is practically impossible to obtain sufficient living material for any extensive work on human tissue, animals were used for the development and standardization of the technic, and normals were determined for these. The human tissue obtained was used to confirm rather than to develop such data, and it was deemed advisable to regard the human tissues as only comparatively normal.

3. Gratz, C. M.: Tensile Strength and Elasticity Tests on Human Fascia Lata, *J. Bone & Joint Surg.* **13**:534-540, 1931.

SELECTION AND DEFINITIONS OF MECHANICAL PROPERTIES

Engineers characterize the strength of elastic diaphragms, such as the tissues under consideration, as "tensile stress and shearing stress." These tissues cannot carry compressive, bending or torsional loads. Tensile stress results from the application of load which is parallel to the direction of the fibers. When the load is in excess of the strength of the tissue, the fibers rupture. This point marks the maximum tensile strength of the tissue.

When stress is not parallel to the direction of the fibers, a shearing stress results. This is caused by forces tending to slide one particle over the other. When a load acts in a direction not parallel to the fibers, there is a combination of shearing stress and tensile stress.

Elasticity.—Elasticity is that property of a body which causes it to resist deformation and afterward recover its original size and shape. The popular conception of elasticity is "stretchability" (as exemplified by rubber). This conception would give the impression of ability to change form, whereas the engineer understands elasticity not as the extent of stretchability but rather as the degree of recovery of original form. To illustrate, if identical unit areas of rubber and steel are subjected to the same amount of stress, the rubber will stretch more, but the resistance of the steel will be greater and with the release of stress it will return more nearly to its original form. Therefore, the elasticity of steel is greater than that of rubber. The standard measure of elasticity is in terms of Young's modulus. The importance of these definitions in this study cannot be too strongly emphasized.

Comment.—Theoretically, it should be possible to determine the elongation of tissues under stress until the point of rupture. Practically, the determinations on the latter part of this scale when tearing begins to take place have been found to be more or less inaccurate. The initial range of elasticity is determined by the location of the point up to which the tissues are truly elastic. The engineering term used for such a point is "proportional limit." A practical term for the description of the initial range terminated by such a point in the case of biologic material would be the "physiologic range of elasticity." This range corresponds on the graphs to the length of the composite graphs plotted, and it will be noted that the uniformity extended to a load corresponding to 500 Kg. per square centimeter (7,100 pounds per square inch).

Of what practical value are the defining and measuring of this initial range of elasticity?

In inorganic materials stress may be applied up to this point and repeated without permanent damage. In biologic structures separation of the fibers follows the application of load in excess of this point, and repair is more difficult than in the case of steel and other structures

in which replacement is possible. Whether rupture takes place in fibrous tissues or a fracture occurs in osseous structures, the result depends on whether or not the load exceeds this range of elasticity.

If two persons are subjected to a similar degree of stress, permanent damage may be sustained by one, while the other may have only a trivial injury. In view of the importance of making a definite prognosis, a competent producing cause of this variation in the degree of injury sustained by two patients is of inestimable value. On the basis of the engineering definition, the physiologic range of elasticity would have been exceeded in the first patient but not in the second. In the first patient the tissues would have lost their power of recovery; in the second, this power would have been unimpaired.

Another clinical phenomenon that is difficult to comprehend is the resistance of tissues without injury to a comparatively large amount of stress, while permanent damage may follow a trifling injury. In this case there are a smaller number of variable factors to be considered than in the previous example, and the natural query is: "What relation has the amount of stress to the damage sustained?" The graphs show that where there is tensile stress alone the elastic limit is not reached as quickly as when a combination of shearing and tensile stress is present. Therefore, a comparatively smaller degree of trauma produces damage beyond recovery by exceeding the physiologic limit of elasticity, if a combination of the two types of stress exists.

TECHNIC

The detailed technic of the methods employed in testing tissue and the methods devised for presenting such data have already been presented.⁴ A brief résumé only will be given here.

A Schopper strength tester was used for the determination of tensile properties. Special clamps and necessary changes were made in the machine for the type of tissues being tested. Special instruments and technic were necessary to determine the cross-section area of the test specimens. The test pieces were 15 mm. long, and their cross-section area usually varied between 1 and 3 sq. m. The load was applied, and the resultant elongation of the test specimens was read at regular intervals. The tests were carried to rupture of the fibers. The result of each test was tabulated in a test record and then plotted in graphic form.

When the test data were thus available, a system of graphs and charts rendered the data available for comparative study. Individual graphs comprising several tests on tissue from one animal were averaged and composite graphs thus obtained. The composite graphs from individual animals were again averaged for two or more animals of the same species, and resulting graphs were regarded as representative of the tissues of one structure from that species.

The details of individual composite graphs are shown in figure 1 for certain tests on the sheep and in figure 2 for certain tests on human tissues. The vertical

4. Gratz, C. M., and Blackberg, S. N.: *Engineering Methods in Medical Research*, *Mechan. Engin.* 57:217-220, 1935.

lines represent the amount of load, and the horizontal lines, the amount of elongation from such a load. The metric system is used throughout, and the load is calculated in kilograms per square centimeter (multiply by 14.2 to change to pounds per square inch). The composite and representative graphs are plotted only to the physiologic limit of elasticity. Representative graphs are alone used in the final summaries (fig. 3), which comprise the data obtained from the study of normal adults. Remarkable similarity between the animals tested and the human material tested is shown by comparison of a representative graph of the species studied (fig. 4).

Comment.—The variations between the individual graphs portray the factors of error in the technic. The total range of all results has been tabulated, but space does not permit the publication of all the data.

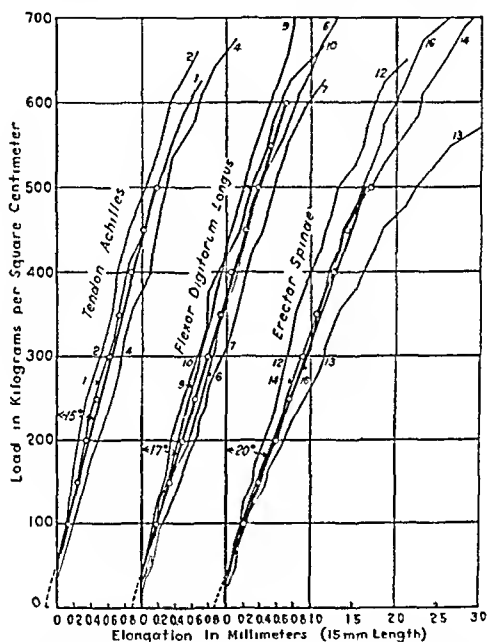


Fig. 1.—Tensile tests of fibrous tissues of an adult sheep.

When this work was commenced, a variation of at least 30 per cent was expected, but much greater accuracy was obtained, the total range and variation between normal adults being in many cases less than 5 per cent.

The deductions made and the conclusions drawn from this study depend primarily on the accuracy of the data presented. All test pieces were prepared and all tests were made by me, with the subsequent preparation of graphs and charts. All data have been rechecked and approved by the workers who were associated with me.

As a result of these determinations on normal adults, the tensile strength, the elasticity and the physiologic range of the limit of elasticity of a representative cross-section of mammals are now available

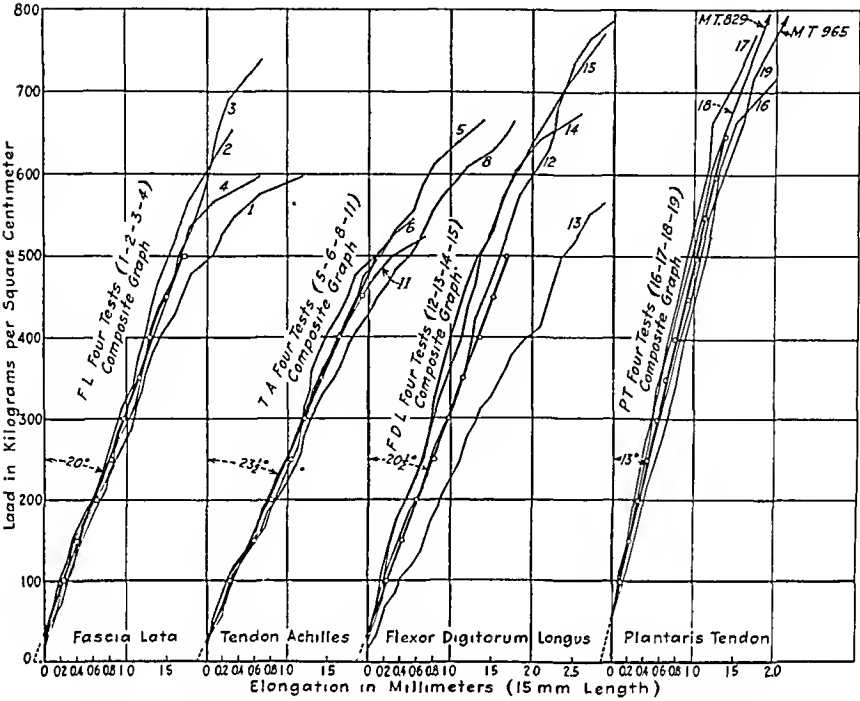


Fig. 2.—Tensile tests of the fibrous tissue of the human adult.

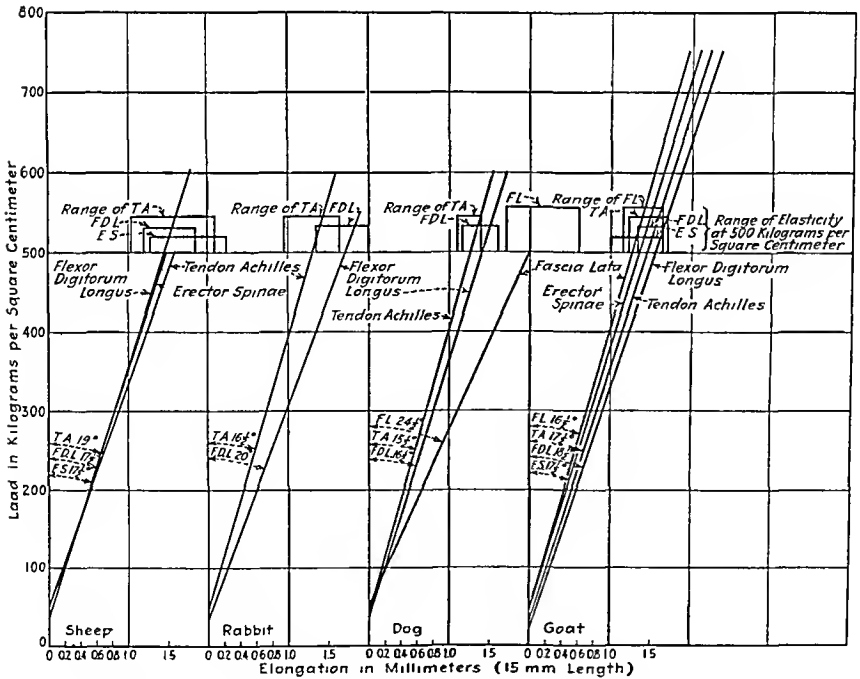


Fig. 3.—Summary chart of test data of species studied.

for study. The criteria are of sufficient accuracy to assume that fibrous tissues of the mammals are essentially alike in these three physiologic properties under normal physiologic requirements. Variations in weight are apparently compensated for by variations in the size of the individual structures. Thus criteria are available for the study of variations due to shear, trauma and other causes.

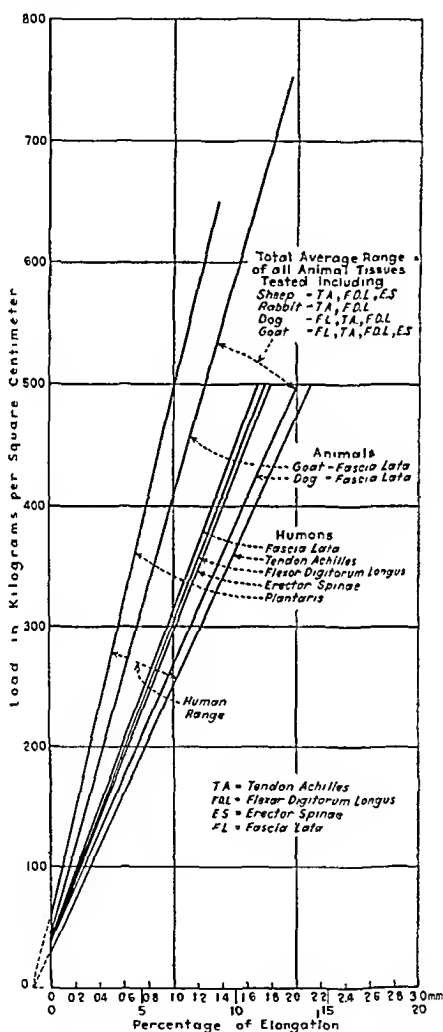


Fig. 4.—Summary of result of tensile tests of fibrous tissues. (Graphs are not plotted beyond proportional limit. Data from tissues resulting in curved graphs are not included.)

CLINICAL ADAPTATIONS OF STRENGTH, ELASTICITY AND PHYSIOLOGIC RANGE OF ELASTICITY

The determinations of strength, the elasticity and the physiologic range of elasticity now available on fibrous tissue of mammals (including man) are of the utmost clinical value.

Tensile Strength.—Certain fibrous tissues were found to withstand stress up to a maximum of 1,476 Kg. per square centimeter (20,959 pounds per square inch). They have a specific gravity of approximately one-seventh that of steel and pound for pound approximate the tensile strength of structural materials. Clinically, however, findings of maximum tensile strength are of importance only if related to the function of these tissues.

Disturbances of the functions of tendons, particularly in the extremities, produce objective findings as well as symptoms and demand clinical study. When injuries to these tissues produce subjective symptoms alone, the diagnosis is difficult. That is particularly true of supportive fibrous tissue in less accessible portions of the body. Clinically, the tensile strength may be regarded as a graphic portrayal of adaptations to their function in body mechanics.

Elasticity.—It must be reemphasized that elasticity is the ability of a structure to withstand stress and to return to its original form after deformation. Of the tissues studied, it was considered that tendons were particularly designed for the transmission of power and that fascia had as its primary function support combined with kinesis. While there are differentiations between the two, they possess a high and markedly similar range of elasticity. Both require the ability to withstand stress and still maintain a relatively constant form. If such properties were not possessed by tendons and fascia, excessive variations in their form would result, leading to a disturbance of body mechanics. It may be noted in passing that the properties of supportive structures in quadrupeds, while in the same relative range, show an elasticity greater than in human beings.

The determinations of elasticity are of sufficient accuracy to be used in estimating the relative elasticity of other structures than the tendons and fascia. Such findings would be of tremendous clinical importance in relation to the circulatory system.

Physiologic Range of Elasticity.—The importance of proportional limits of elasticity was previously discussed; this is regarded as the terminal point in the physiologic range of elasticity. The tissues studied maintained their elasticity to a minimum tensile strength of 500 Kg. per square centimeter (7,100 pounds per square inch). Although the elasticity of many tissues exceeded this point, the fact that so high a minimum existed was one of the most important observations of the entire work.

Theoretically, if such tissues were subjected to a stress parallel to the direction of their fibers and if such force were within this limit, no separation of the fibers would take place. The determination of

this minimum range of elasticity makes available a definite point at which variations beyond the physiologic limit of elasticity may well be the long looked for explanation of the permanency of certain injuries.

Consistency of the Findings.—Figures 3 and 4 show that the similarity of animal and human tissue studied is remarkably consistent in tensile strength, elasticity and proportional limit. What does this consistency indicate?

These findings may be regarded as determinations of the mechanical form, just as histology is a study of minute structures and anatomy a study of the gross structure. As their functions probably determine their histologic and anatomic form, so in the same manner their functions probably determine the tensile and elastic properties. The paralleling of these studies indicates that any consideration of body mechanics should include study of the fibrous tissues from every angle.

The standard textbooks of anatomy contain scant discussion on the fibrous tissues, with the exception of the tendons. Comparative histologic studies of fibrous tissues are rare in English and American textbooks. The physiologist has accorded these tissues less study than he has the muscles. Finally, one might briefly review any book on traumatic or orthopedic surgery and compare the discussion on the osseous structures with that devoted to the surgery of the fascial planes. The functions of these tissues seemed to be relatively forgotten in mesodermal mechanics. A study of the fascial planes of any portion of the body, therefore, should when clinically applied lead to a marked improvement in the results of surgical treatment of the particular part selected. Kanavel's⁵ study of the fascial spaces of the hand in relation to infection has completely revolutionized the clinical treatment of this member. In the words of Steindler:⁶ "Unless we have a pretty clear conception of the functional mechanics of the soft structures which form part of the locomotor system we will not be able to go much further in the management of the legion of conditions which arise from the disturbances of these structures."

Application to Pain Low in the Back.—The preliminary report of the study of the functions of the fascial planes in relation to pain low in the back has already been made,⁶ and the findings so reported have been clinically applied since April 1935. Clinically it is believed that impaired functions of the fascial planes of the lower part of the back and the thigh may be caused by fascial adhesions interfering with the normal translatory motion of the muscles which the planes enclose and secondarily involving the nerves.

5. Kanavel, Allen B.: *Infections of the Hand*, Philadelphia, Lea & Febiger, 1925. Steindler, Arthur, in discussion on Gratz.⁶

6. Gratz, C. M.: *Biomechanics: A New Method of Studying Physical Disabilities*, Arch. Phys. Therapy **17**:145-150, 1936.

The tissues selected for the biomechanical study of this work included the erector spinae and also the fascia lata. Histologically, variations (figs. 5 and 6) in the arrangement of the fibers of these two tissues were noted. It was found, however, that these tissues, like tendons, were covered with a mesothelial layer of cells (fig. 6). This is regarded as a functional adaptation of the fascial planes, permitting movements between groups of muscles which they enclose. The fascial

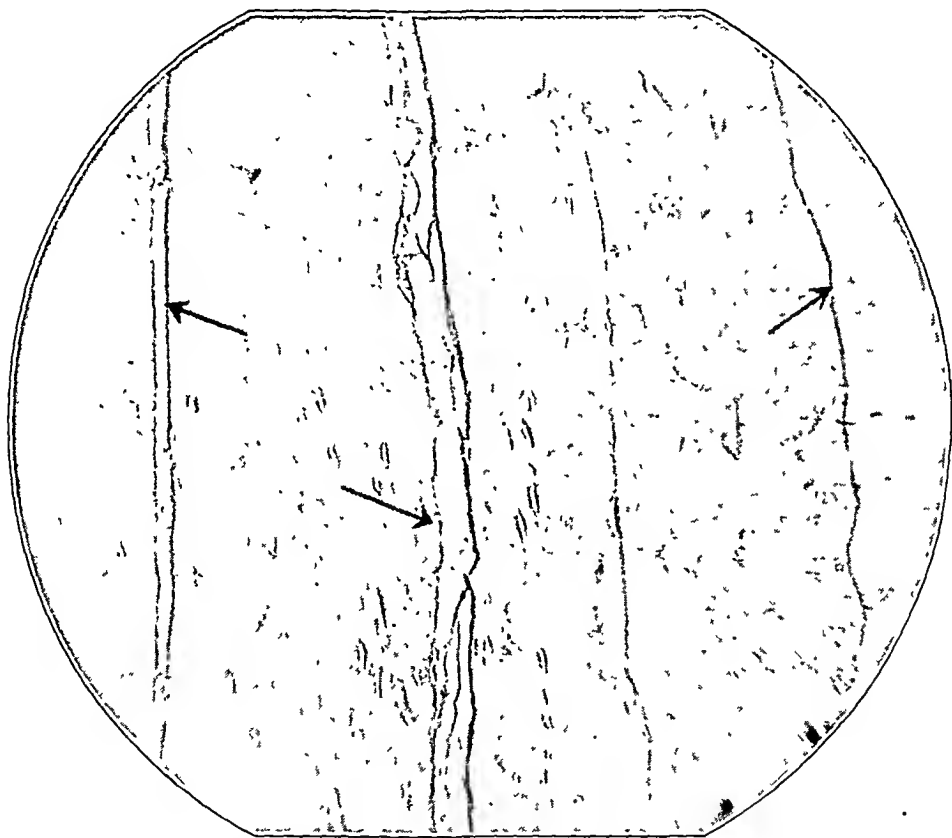


Fig. 5.—Photomicrograph of the human erector spinae. The heavy fibrous bands are shown and also the spaces between them. The fascial bundles are approximately parallel to one another.

spaces thus form joints between muscles (fig. 7) which transmit nerves and blood vessels from the central nervous system and the heart to the periphery of the body.

The lymphatic circulation is also intimately connected with the fascial spaces. This may be of vast importance not only in acute infections but in chronic rheumatic and arthritic conditions. The strength of the fibers of fascia thus serves to protect the nerves and blood vessels in addition to transmitting power between mesodermal

tissues. In normal locomotion these functions are probably performed with an adequate factor of safety. Anatomic studies on cadavers⁶ in which air was injected into the fascial spaces showed free gliding motion between the nerves and the fascial spaces surrounding them. Anatomic studies on other cadavers (fig. 8) showed firm adhesions between the nerves and their fascial covering, which were easily demonstrated and photographed by using the same technic. Histologic studies on the mesothelial cells of arthritic patients showed a variation in the form of these cells which may correspond to the impaired functions of the muscles and the pain which these

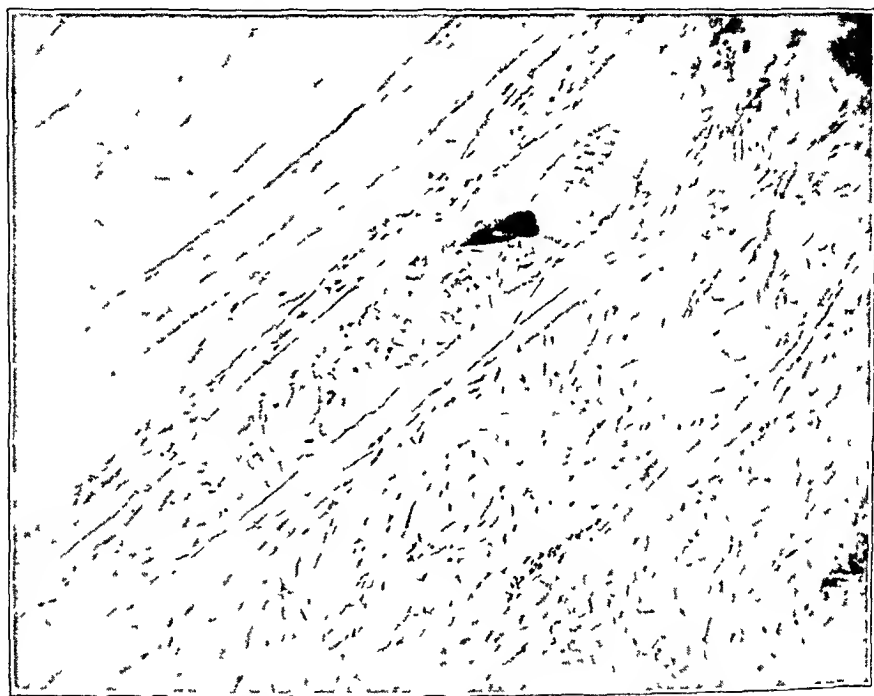


Fig. 6—The mesothelial covering of fascial fibers. Photomicrograph of normal human fascia lata (from the lower part of the thigh, a man, 32 years of age). Between the fibrous tissue bundles delicate strands may be seen. These are lined by flattened mesothelial cells. Parallel fibers will be noted in certain sections, and the central portion of the photomicrograph shows strands of fibers with an irregular arrangement.

patients had on normal movements. Hence it is believed that fascial adhesions may be the cause of limitation of motion and also of pain in certain cases of pain low in the back and of sciatica. Following the same technic as was developed in this research, air has been used clinically as a contrast medium to visualize the fascial spaces.⁷ Such

7. Gratz, C. M: Air Injection of the Fascial Spaces. A New Method of Soft Tissue Roentgenography, *Am. J. Roentgenol.* **35**:750-751, 1936

roentgenograms are technically known as pneumofasciagrams. Roentgenographic variations between the normal and the arthritic patient have been noted which are believed to be due to fascial adhesions.

By the method described it has been possible to correlate this entire research work and combine it with roentgenographic studies for a new approach to the study of pain low in the back. Therapeutically, it was noted that the injection of air into the fascial spaces produced an increased range of motion of the parts treated. When this had been done in highly selected cases and combined with muscle training and physical therapy, the increased range of motion persisted. In addition, a gratifying relief from symptoms was obtained. This method of study has been regarded as being primarily largely diagnostic, but a working

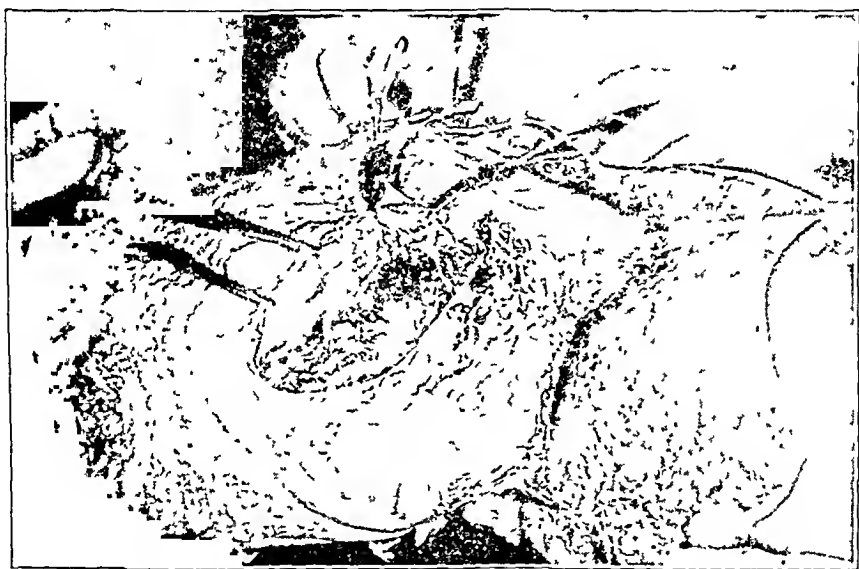


Fig. 7.—The fascial joint between the gluteus muscles. The mesothelial covering of the fascia is shown as the fascial plane is held backward by the clamps. A bursa is noted between the two fascial planes.

report of the clinical features of this method of treating fascial adhesions is now being prepared. It is believed that this method, when perfected, will aid in localizing the pathologic process causing the symptoms and thus add to the accuracy of the surgical approach for its correction.

The rôle of trauma as the causative factor of pain low in the back and arthritis has been most difficult to explain, and in medicolegal cases particularly its importance is very great. A careful study of certain of these cases in which the foregoing concepts were used has led me personally to believe that trauma, particularly if it results in a shearing force, may tear certain fibers in the lower part of the back

or thigh and produce a secondary effect on the nerves transversing the fascial spaces. It should, however, be emphasized that the clinical applications of the concepts are not as yet sufficiently perfected to warrant general application and that injections into the fascial spaces for diagnostic and therapeutic purposes should be made only after a most thorough study of the anatomy of these spaces and a most careful clinical examination of the patient. The dangers of infection and embolism should be constantly in mind. Correlation of these studies with clinical procedures devised by other clinicians for treatment of pain low in the back and sciatica are discussed later in this paper. A remarkable similarity exists with the work of Penfield^{7a} in his treatment of post-



Fig. 8.—Adhesions involving the sciatic nerve. Air was injected into the fascial planes of this cadaver before dissection. Firm adhesions across the sciatic nerve are noted at the point shown by the arrow. There is bulging of the fascial covering of the sciatic nerve on either side of the adhesions.

traumatic headache by lumbar insufflation of air. His belief that "the abnormality, whatever it is, is obviously a mechanical one" and his mention of fine meningeal adhesions closely parallels the present explanation of obscure pain elsewhere.

7a. Penfield, Wilder: Chronic Meningeal (Post-Traumatic) Headache and Its Specific Treatment by Lumbar Air Insufflation; Encephalography. *Surg., Gynec. & Obst.* **45**:747-759, 1927. Penfield, Wilder, and Norcross, Nathan C.: Subdural Traction and Posttraumatic Headache, *Arch. Neurol. & Psychiat.* **36**: 75-94 (July) 1936.

VARIATIONS FROM NORMAL

The consistency of normal findings facilitated the study of forces causing variations from the normal.

Shear and Trauma.—Shear is a comparatively new word in surgery. In the literature reviewed Steindler's epoch-making book contained the only intensive study of the subject.⁸ Shear has been studied by engineers for many years. The application of such a study to biologic material brings to light many findings of clinical value. Shear has been previously defined as being caused by any stress which tends to slide one portion of the test substance over the other. The engineering determinations are based on the study of inanimate objects.

Shear in biologic material should be of even greater interest, since the fibers in connective tissue depend for their nourishment on the cells between the individual fibers. Shearing stress would cause greater destruction of these cells than of the fibers themselves, thus causing more damage in biologic than in inanimate material. This fact adds to the interest of the study of shear in surgical procedures involving biologic tissues.

The normal being established, it is now possible to study shear phenomena and portray results graphically. These have been plotted in standard form and are shown in figure 9. Variations from the normal are so marked that definite conclusions would seem to be justified.

The first graphic portrayal of shear phenomenon is shown in figure 9A. All details of testing were the same except that the tissues tested were cut diagonally in increasing amounts from tests 1 to 6. This necessarily produced a shearing stress when load was applied in the direction of the arrows. The same phenomenon results when a living fibrous transplant is carelessly cut, the fibers not being parallel. Clinically, if fibrous tissues were securely fastened to two structures and then submitted to a stress not in the direction of the fibers, shear would result in addition to the tensile stress.

What is the effect on the physical properties of combining these two types of stress?

Figure 2 shows the average maximum tensile strength of the tendo Achillis to be 610 Kg. per square centimeter, with a maximum variation of 14 per cent. The maximum strength of the six pieces in which shear and tensile stress were combined varied between 165 and 428 Kg. per square centimeter. There is no regularity of elongation shown graphically by the lines. It is therefore impossible to obtain an average for results as was accomplished when tensile stress alone was studied. Tests 1 and 2 indicate that the tissues stretched irregularly and that

8. Steindler, Arthur: *Mechanics of Normal and Pathological Locomotion in Man*, Springfield, Ill., Charles C. Thomas, Publisher, 1935.

their maximum strength was far short of the normal. In the tissues of the remaining four tests the elongation was excessive and the maximum tensile strength much less. Thus, in the six combination stresses studied in this group no elastic limit was obtainable, and the physiologic range of elasticity was reduced to a vanishing point.

Various types of shear were studied, including transversely cut and irregularly cut specimens. In all cases there was marked variation in the elastic and tensile properties, and in none of these groups could a physiologic limit of elasticity be determined. It is therefore shown that combinations of shearing and tensile stress are a competent producing cause of permanent changes in the tissues even if a minimum

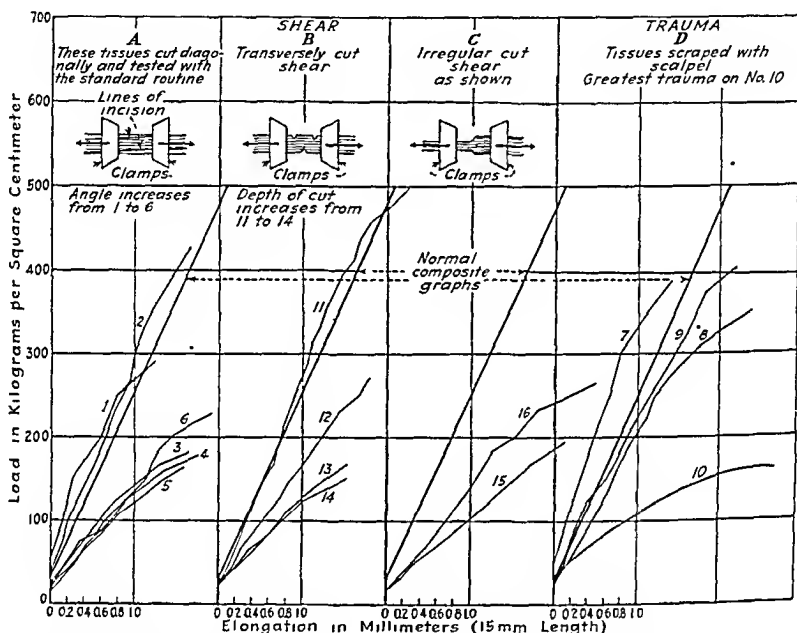


Fig. 9.—Graphic portrayal of the effects of shear and trauma on the human tendo Achillis of an adult.

of stress is applied. The extent of damage to tissues is proportional to variations in applying stress rather than to the amount of stress applied. These findings are of interest when applied to the erector spinae in pain low in the back and also in relation to the fasciae surrounding the sciatic nerve.

Shearing stress occurring in normal body mechanics would tend to produce marked damage to the tissues were the body not designed to counteract and minimize it. Since certain structures perform functions in various directions, fibrous tissues are logically so arranged as to perform these functions without the development of shear.

Microscopic sections of fascia lata (fig. 6) show a composite arrangement for such a purpose. Macroscopic examination of structures, such as a conjoined tendon, also shows a composite arrangement. These two are examples of function determining form and being arranged so as to avoid shear phenomena.

I shall consider the mechanics of the knee in the same terms as I have considered other structures. The quadriceps tendon and the patellar ligament transmit power in one plane only. How do these structures function when the knee is flexed? It would seem that forces pulling over the knee joint when in a flexed position would necessarily result in a shear phenomenon. Nature counteracts this through the structure of the patella. It will be found that the quadriceps tendon above and the patellar ligament below are attached to the patella so as to reduce to a minimum any shearing force. When a person is standing upright with considerable tension in the region of the knee, like a football player set to receive a pass, a shearing force is combined with tensile stress when such a person is "tackled." The result is a combination of tensile and of shearing stress and may explain the frequency of injuries in football players, particularly in the region of the knee.

Macroscopically, the structure of the sesamoid bones and the changes mentioned in certain tendons would seem to conform to nature's functional adaptation to eliminate or reduce the shear phenomenon. It would further seem that when the body is subjected to trauma which may result in a combination of tensile and of shearing stress such a combination may account for the severity in certain accidents.

Graphic portrayal of the effect of trauma is presented in figure 9 *D*. On reviewing the early tests it was found that the graphs showed all the effects of shear and trauma, as shown in this illustration. When the technic was revised and variations due to these two forces were reduced to a minimum, the normals presented were available. It is felt that the graphic portrayal of these two forces is a fair presentation of the effects of shear and trauma, as observed throughout the preparation of the entire work.

ADAPTATIONS IN REPARATIVE SURGERY

It must be remembered that the tissues studied are normally self-repairing and self-adjusting within certain limits. The physical properties of biologic material are regarded as being evolved in response to functional demands. The surgical adaptations are similarly considered in relation to the functions of repair and are correlated with this function. The monumental work of Hawley⁹ in correlating surgical pro-

9. Hawley, George W.: *Biological Basis of Surgery, Particularly Orthopedic Surgery*, Am. J. Surg. **31**:438-453, 1936.

cedures with the biologic aspects of human tissue is particularly appropriate in guiding us in the application of these findings to clinical procedures.

Fibroplasia in the Process of Repair.—In the repair of muscles, fibrous tissue and bone, fibroplasia is noted in all three. It has been commonly observed microscopically that muscles repair themselves after injury by the formation of fibrous scar tissue. It is often found that the strength of such repair is greater than of the muscles themselves.

Fibroplasia is responsible for the unassisted repair of injured tendons and fasciae and occurs in the repair of osseous structures. Ackerson gave a detailed description of the sequence of mesodermal metaplasia after rupture of the supraspinatous tendon of the shoulder.

Fibrous tissue is formed in the unassisted repair of mesodermal deformities, and it is of interest to know that its formation in such localities parallels the normal development during growth. Wassermann,¹⁰ citing Levy, said:

In simple severing of the tendon the arrangement of the cells and fibers in the young germinal tissues, even in the transitional stage, corresponded to the traction forces which are the natural result of movements of the foot and leg through the action of the flexors of the thigh transmitted to the fascia and through simple stretching of the fascia. . . . Levy's work showed a second important fact, namely, that in the absence of traction on the young germinal tissue there is also quantitative reduction of connective tissue formation in comparison with that noted in simple severing of the tendon. . . . Levy observed that the tension in certain directions influenced the direction of growth of the cells and their form as they proceeded to grow; he also observed that this tension influenced the intensity of fibril formation. These findings Weiss corroborated in every detail. The fact that Trierpel and Weiss agree seems especially important. . . . The conclusion is that we do not know to what extent mechanical demands play a part in genesis, but we are justified in assuming that the arrangement of the elastic fibers and the measure of their development are subject to the same influences as are similar processes in the non elastic elements of the connective tissue.

Fibroplasia in the normal process of repair of mesodermal structures and of the tissues so formed varies according to the functional demands on it in the same way as during normal growth. Surgical repair, which permits early application of tension and hence stimulates fibroplasia, could be expected to result in much more rapid return to normal function.

Fibroplasia in Surgical Repair.—The ultimate success of any reparative surgical procedure depends primarily on the permanency and strength of union between the coaptated tissues, assuming that the union is physiologically correct. The strength of such repair, if pre-

10. Wassermann, F.: Die Histogenese als abhängige Differenzierung in von Möllendorf, Wilhelm: Handbuch der mikroskopischen Anatomie des Menschen, Berlin, Julius Springer, 1929, vol. 1, pp. 727-735.

pared sutures are used after the first few days, depends on the newly formed fibrous tissues rather than on the sutures themselves. Howes¹¹ proved this and graphically portrayed the strength of the healing wound in relation to fibroplasia. What then is the function of prepared sutures?

Except during the first few days, the strength of repair does not depend on the sutures themselves. When nonabsorbable sutures are used they are found to coaptate the tissues for a variable length of time. If such sutures are inserted under tension, they cause definite changes in the tissues in which they are embedded. This may result in weakening of the suture line with corresponding inaccuracies in coaptation. This weakening will vary directly with the elasticity of tissues in which such sutures are placed; hence tension on the sutures may set up a vicious circle. Even if such sutures are advantageously placed, for the reasons stated they may prove insufficient to counteract the retraction of the muscles and fibrous tissue which they are required to hold.

Absorbable sutures play the same rôle, except that with their use there is the additional factor of progressive loss of tensile strength of varying intensity, which under certain circumstances may impair the coaptation of the tissues sutured. Both play a passive rôle, and their ability to hold the tissues is no greater than the strength of their host tissues. Therefore, as Howes suggested,¹² a definite technic of suturing should be developed which would reduce to a minimum any damage done to their host tissues.

The normal graphs contrasted with the shear graphs indicate what the ideal technic should be. If fibrous tissue is subjected to a stress not at right angles to its cross-section, excessive elongation of the structure occurs, with a resulting deformity or a pulling out of the suture. This is the fallacy of most of the methods of suturing which have been devised to repair tendons. Moreover, most sutures are inserted in such a manner that they play an entirely passive rôle in holding the tissues. The coaptation is seldom designed to withstand or even to approximate the original function of the tissues involved. A new method of repair embodying these principles is being published.

Theoretically, living sutures offer a greater possibility of establishing early approximation of fibrous tissues because they supply in part the mesodermal structure which must be regenerated. They may be safely held under tension and thus approximate the normal functions of the involved area. The fundamental difference between living sutures and

11. Howes, E. L.: Factors Determining the Loss of Strength of Catgut When Embedded in Tissue, *J. A. M. A.* **90**:530-532 (Feb. 18) 1928.

12. Howes, E. L.: Strength of Wound Sutures with Catgut and Silk, *Surg., Gynec. & Obst.* **57**:309-317, 1933.

prepared ones (either absorbable or nonabsorbable) is that the former take an active part in the desired union of the tissues, in contradistinction to the passive rôle of the prepared suture.

CLASSIFICATION AND SELECTION OF CASES FOR FASCIAL TRANSPLANTATION

Direct transplantation of fibrous tissue is indicated in cases in which the strength of fibroplasia may clinically be of insufficient strength. Such a method supplements the strength of fibroplasia with the strength of the transplant.

In the words of Neuhof and Hirschfeld:¹³ "Fascial transplants offer a wider scope in reparative surgery and a greater field of usefulness than the other forms of transplantation." As the selection of cases for transplantation depends primarily on the strength of the repair needed, the comparative strength of the tissues involved would seem to be a logical guide to assist in selecting individual cases. Therefore, the problem resolves itself into a study of the processes of repair in bone, muscle and fibrous tissues in relation to their strength.

Study of the permutations and combinations between the groups of connective tissue structures should enable the surgeon to establish principles on which the selection of cases could be successfully based. Of the three groups, muscle has the weakest tensile properties, and bone the strongest, and the tensile properties of fibrous tissues lies between these two extremes.

Certain physical properties of fibrous tissues have now been determined and compared, thus assisting in such a selection. The six possible combinations arranged in relative order of strength are: (1) muscle to muscle, (2) muscle to fibrous tissue, (3) muscle to bone, (4) fibrous tissue to fibrous tissue, (5) fibrous tissue to bone and (6) bone to bone.

Fibroplasia between muscles is often stronger than the muscles themselves; so transplantation of any tissue should seldom be necessary except in cases in which there is a marked destruction of the muscle itself.

The strength of fibroplasia is frequently insufficient in the union between muscle and fibrous tissue. In certain cases of repair of hernia transplantation of fibrous tissue is indicated to replace tissues that are no longer present. In other cases tension is necessarily placed on the suture line. In both groups reenforcement of the repair by fibrous tissue transplantation is frequently indicated, especially in cases in which the hernia has recurred after treatment.

13. Neuhof, Harold, and Hirschfeld, Samuel: *The Transplantation of Tissues*, New York, D. Appleton & Co., 1923.

In every organism muscle is attached to bone by fibrous tissue. When union is desired between muscle and bone, the transplantation of fibrous tissues for such repair would be physiologically correct in selected cases.

Is the transplantation of fibrous tissues to fibrous tissues the physiologic ideal? When tendons are severed, the tonus of the muscle to which they are attached and their own high elasticity may result in marked retraction. The tensile properties and elasticity which fibrous tissues have been shown to possess make them ideal for such a repair. The difficulties encountered in using prepared sutures have already been shown. Fibroplasia is usually of sufficient strength if operation is performed early, but in certain cases in which marked retraction has taken place reenforcement of the repair by transplanted tissues is frequently indicated.

Union between fibrous tissue and bone should be stronger than between fibrous tissues themselves. It is necessary, therefore, to secure a physiologic union sufficiently strong to withstand clinically the stress to which the union may be subjected. Transplanted fibrous tissue is the physiologic choice to supplement the strength of scar tissue in many cases.

In a few cases union between osseous structures may require tissues of greater tensile strength than that possessed by the fibrous tissues, and in such cases foreign material or bone grafts have frequently proved successful. The splendid work of Albee,¹⁴ based on sound biologic principles, has solved many of the difficulties previously encountered in this group. In certain cases transplantation of fibrous tissue is indicated¹⁵ as a supplement to plastic repair of bone. In the evolution of joints, fibrous tissues are developed. Therefore, in cases in which union is desired or in which reenforcement of joints with motion is required, transplantation of fibrous tissue would seem to be physiologically indicated. The high tensile strength which fibrous tissues have been shown to possess indicates that the possibilities of using them in plastic repair of bone are just beginning to be realized.

The variable tensile strength necessary in repair requires a variety of methods to achieve permanent results. The strength of the tissues coapted would be weakest in union between muscle and muscle and strongest between bone and bone. In cases of the former type transplantation of any tissue is seldom indicated, whereas in certain cases of the latter group a bone graft or even foreign material may be required to supplement the strength of repair.

14. Albee, Fred H.: *Orthopedic and Reconstruction Surgery*, Philadelphia, W. B. Saunders Company, 1921.

15. Gratz, C. M., and Robison, Richard P.: *Living Sutures as a Supplement to Plastic Bone Surgery*, *Am. J. Surg.* **26**:362-367, 1934.

Between these two extremes lie the group of cases in which transplantation of fibrous tissue is more commonly indicated. It should be emphasized, however, that the strength of any repair is no greater than the strength of the host tissues, and the method of repair should be so devised as to conform with the normal processes of repair which the body possesses.

From references already made to the metaplasia between mesodermal structures, it seems logical to assume that transplanted fibrous tissues would unite to bone, muscle and other fibrous tissues. Clinical work herewith reviewed shows the difficulties encountered and the progress made clinically in securing firm union between the transplant and these structures.

McArthur in 1901¹⁶ was one of the first successfully to transplant fibrous tissues for surgical repair. Kleinschmidt¹⁷ did a large amount of experimental work on the transplantation of fascia. He used three groups of rabbits, twenty-three animals in all, and showed that fascia remained alive and showed changes in its structures in response to the functional demands made on it. This observation was of profound significance as it showed that the transplanted tissue paralleled fibroplasia and fibrous tissue formed during normal growth.

Kleinschmidt also advised the longitudinal insertion of the fascial tissues and made the important observation that when transplants were placed beneath the skin, where they were not subject to tension, they showed little replacement.

Unfortunately, the early surgical technic did not strictly conform to the physiologic principles enunciated by these workers. Patch transplants were generally used and held in position by prepared sutures. Such transplants were not cut parallel to the fibers. On the application of stress after transplantation a combination of shearing stress and tensile stress may result in disintegration of the transplant. This would parallel the shear phenomenon graphically shown in figure 9 and would account for the partial failure of many patch transplantations.

Gallie and LeMesurier¹⁸ noted that in certain cases firm union resulted between fibrous tissues and bone in their operation for tenodesis. In other cases separation occurred between tendon and bone. As a result of these observations, they used fibrous tissues cut parallel to

16. McArthur, L. L.: Autoplastic Suture in Hernia and Other Diastases, *J. A. M. A.* **37**:1162-1165 (Nov. 2) 1901.

17. Kleinschmidt, O.: Experimental Investigations Concerning the Histological Changes in Structures in Freely Transplanted Fascia Lata and Proof of the Viability of This Tissue as Shown by Vital Staining, *Arch. f. klin. Chir.* **104**: 933-954, 1914.

18. Gallie, W. E., and LeMesurier, A. B.: The Transplantation of the Fibrous Tissues in the Repair of Anatomical Defects, *Brit. J. Surg.* **12**:289-320, 1924.

the direction of the fibers as a suture. The technic became known as living suture surgery. All fat and fibrous tissues were removed, as these interfered with the formation of lymphatics around the transplant, cutting off the lymphatic supply. Trauma during transplantation was reduced by the use of special instruments. Shear phenomena were thus minimized, and the growth of the transplant facilitated in its new position. The work of Gallie and LeMesurier¹⁸ greatly improved the results in transplantation of fibrous tissue, and many new fields were opened for its use.

The present status of living suture surgery is concisely stated by Bunnell¹⁹ on the basis of his vast clinical experience: "Free grafts of fascia and tendon have normal appearance and normal function over years, and hypertrophy in response to use. They grow solidly to bone, muscle and tendon, if properly contacted." The requisites of proper contacting of the transplanted tissues in the terms which are being used will be fully described later.

What clinical results have been attained in the groups before mentioned? A review of the literature has disclosed no report of a case in which transplantation has been necessary in repairing defects in the muscles themselves.

The surgical repair of hernia requires union between muscle and fibrous tissue. Living sutures have proved most successful in this type of repair. The work reported by Gallie and LeMesurier and also by Coley and Burke²⁰ deserves particular mention. Success has been achieved in the treatment of recurring hernia and in cases in which large transplantations are required to replace tissues no longer present.

In the union of muscle to bone one brilliant example of using a large transplant is the operation of Mayer²¹ by which a paralyzed deltoid muscle is replaced by the action of the trapezius muscle. Fascia lata is attached to this muscle, transmitting its power to its desired insertion in the humerus.

Living sutures have been particularly advantageous when used to repair defects in the fibrous tissues themselves. The clinical achievements of Gallie and LeMesurier¹⁸ and of Bunnell¹⁹ are noteworthy con-

19. Bunnell, S.: Fascial Graft for Dislocation of Acromioclavicular Joint, *Surg., Gynec. & Obst.* **46**:563-564, 1928.

20. Coley, B. L., and Burke, E.: Operative Treatment of Hernia by Living Sutures, *Am. J. Surg.* **2**:1-10, 1927.

21. Mayer, Leo: Physiological Methods of Tendon Transplantation, *Surg., Gynec. & Obst.* **22**:182-197, 1916; Physiological Method of Tendon Transplantation, *ibid.* **33**:528-543, 1921; Transplantation of the Trapezius for Paralysis of the Abductors of the Arm, *J. Bone & Joint Surg.* **9**:412-420, 1927.

tributions in this field. The experimental work of Mason and Shearon²² also deserves particular attention.

Union between fibrous tissue and bone was first noted in Gallie and LeMesurier's¹⁸ work on tenodesis. The transplantation of tendons to new osseous insertions has also proved clinically successful. Repair or transplantation of tendons in the lower extremities must be strong enough to transmit the necessary stresses in weight bearing. Transplants of fibrous tissue have been shown to be of sufficient tensile strength to repair ruptured patellar ligaments and quadriceps tendon, in which case the sutures are embedded in the tibia or patella on one side and in the ligaments on the other.

When union is desired between osseous structures, living sutures have been used to supplement bone grafts and also independently. Patterson²³ has employed fascia lata to supplement plastic repair of the tibia and has also made use of the same tissue without bone graft. Ober's²⁴ operation for repair of a fracture of the patella utilizes quadriceps tendon. Transplantation of fibrous tissue has also proved of value in reenforcing joints and repairing dislocations of bone. The work of Henderson,²⁵ Gallie and LeMesurier,¹⁸ Nicola²⁶ and myself²⁷ for the surgical repair of recurring dislocation gives clinical examples. The technic of Bunnell¹⁹ in repairing separation of the acromioclavicular joint is another example.

These examples show the successful use of transplantation in certain of the groups mentioned and may assist in selecting cases for transplantation. The fundamental data presented on the relative strength of tissues may be of aid in determining not only the strength of the transplant but that of the tissues in which it is embedded.

22. Mason, M. L., and Shearon, C.: Process of Tendon Repair: Experimental Study of Tendon Suture and Tendon Graft, *Arch. Surg.* **25**:615-692 (Oct.) 1932.

23. Patterson, R. H.: Internal Fixation of Fractures and Dislocation by Use of Human Fascial Suture, *Ann. Surg.* **88**:879-884, 1928.

24. Ober, Frank R.: Fracture of the Patella: New Operation, *J. Bone & Joint Surg.* **14**:640-642, 1932.

25. Henderson, M. S.: Habitual Dislocation of the Shoulder, *J. A. M. A.* **95**:1653-1658 (Nov. 29) 1930.

26. Nicola, T.: Recurrent Anterior Dislocation of the Shoulder: A New Operation, *J. Bone & Joint Surg.* **11**:128-132, 1929.

27. Gratz, C. M., and Robison, Richard P.: Intra-Articular Stabilization for Recurring Dislocation of the Shoulder: Technique of Suspension to Acromium by Autogenous Fascia Lata Suture, *Am. J. Surg.* **15**:71-74, 1932. Gratz, C. M.: Multiplex Graft Technique for Extra-Articular Arthrodesis of the Spine, *Surg., Gynec. & Obst.* **48**:119-123, 1929.

SELECTION OF TISSUES FOR TRANSPLANTATION

The literature shows that there is a marked divergence of opinion as to which fibrous tissues are most suitable for transplantation. Fascia lata has been most frequently used. Functionally, fascia lata is designed for the transmission of tensile stress in various directions. A suture is used for the transmission of stress in one direction only. Fascia lata showed the greatest variations, and the histologic study showed that its fibers were often compositely arranged. The natural conclusion would seem to be that its availability rather than its physical properties has governed its choice. Henderson²⁵ used fascia lata for tenosuspension of the shoulder, but later found it unsatisfactory and used peroneus longus tendon. Plantaris tendon has also been used successfully as a suture. The remarkable consistency of the physical properties of all the tissues studied shows that if the fibers are arranged parallel to one another they should be of approximately equal value for transplantation. A markedly composite structure would be expected to have poorer tensile properties than one with exactly parallel fibers. Almost all tendinous structures, including the erector spinae of the back and the aponeuroses of the external oblique muscle, have proved satisfactory. This finding enlarges the source of supply and suggests many new locations from which transplants can be obtained. It cannot, however, be emphasized too strongly that fibrous tissue should not be removed from locations where its removal might harm the patient.

It is always desirable to remove the suture from the site of operation, thus eliminating an additional incision and scar. The operation of Ober,²⁴ using the quadriceps tendon for the repair of a fractured patella, is an example of this. I have used a free graft of periosteum taken from the tibia to supplement a bone graft of the tibia. In this particular case there was recurring nonunion after a first bone graft, and the second operation was so designed that in addition to a powerful bone graft further physiologic security was given by the use of strips of periosteum as sutures to hold the bone graft in position.

Periosteum has comparatively poor tensile properties but was used to form a mesodermal bridge between the host and scion tissues with good result. I have also used the erector spinae tendon as a supplement to spinal graft of the lumbosacral angle and lumbar region of the spine. The experimental work of Levering,²⁸ based on the use of peritoneum and the suggestion that the sack be used in the repair of hernia, is one of the recent contributions in this field. The successful clinical use

28. Levering, J. Walter: *The Use of Peritoneum in the Repair of Inguinal Hernia*, *Ann. Surg.* **101**:550-553, 1935.

of the tendon of the triceps muscle to repair a fracture of the olecranon has been reported by Rombold.²⁹

It is believed that an anatomic study of the fibrous tissues will permit the removal of the transplant from the site of the operation in many more locations than have been reported at the present time. Anatomic studies are already under way which may lead to future progress along these lines. It is of tremendous advantage to both the surgeon and the patient if an extra incision can be avoided.

However, the tensile strength of the transplant is only one of the many factors to be considered in selecting the suture. There is also a marked variation in the size of sutures that have been used. One of the smallest reported was a strip of aponeurosis of the external oblique muscle about $\frac{1}{8}$ inch (2.5 mm.) in width (Adair³⁰). In the study of the external oblique muscle it was found that the average thickness of this structure in the human beings studied was 0.2 mm.

Gallie and LeMesurier,¹⁸ in the repair of the patellar ligament, removed a longitudinal half of the tendo Achillis and divided it into two portions, using each as a transplant. Basing my calculations on data obtained in preparing these tests, I found the approximate cross-section of such a suture to be at least 15 sq. mm., or about thirty times the size of the sutures used by Adair. In addition, the tensile properties of the tendo Achillis per unit area are much greater than those of the aponeurosis of the external oblique muscle. While these two examples are the extremes reported in the literature, it is realized that a great many factors, many of which have not yet been determined, will decide the exact size of the suture necessary.

Many surgeons have used sutures of intermediate size. Dutta³¹ used a strip of the aponeurosis of the external oblique muscle 1.1 cm. in width for the repair of hernia. Barr³² used fascia lata for the same operation and endeavored to have the strip about 1 cm. in width. Bunnell,¹⁹ in the repair of separation of the acromioclavicular joint, used a strip of fascia lata about 1 cm. in width. Hodgkins³³ utilized a strip of fibrous tissue from the sheath of the rectus muscle about 6.5 mm. in width. Henderson²⁵ used the entire tendon of the peroneus longus

29. Rombold, Charles: A New Operative Treatment for Fracture of the Olecranon, *J. Bone & Joint Surg.* **16**:947-950, 1934.

30. Adair, F.: Use of Aponeurosis of External Oblique as Source of Living Suture for Inguinal Herniotomy, *J. A. M. A.* **82**:629-630 (Feb. 23) 1924.

31. Dutta, P. C.: Surgery of Fascial Transplantation with Illustrative Cases, *Indian M. Gaz.* **67**:326-330, 1932.

32. Barr, E. O.: Fascial Suture Repair of Hernia, *Virginia M. Monthly* **56**:328-330, 1929.

33. Hodgkins, E. M.: New Method of Inguinal Herniorrhaphy with Living Fascial Sutures Obtained from Rectus Sheath, *Surg., Gynec. & Obst.* **47**:831-836, 1928.

muscle for tenosuspension of the shoulder. These examples are sufficient to show that there is a wide variation in the size of suture used.

SIZE OF A SUTURE

The study of the forces that cause variations in the strength of fibrous tissue as well as the comparative determinations of tensile properties gives definite aid to the surgeon in determining the size of a suture. Fascia lata and the sheath of the rectus muscle are composite tissues designed for transmission of stress in varying directions. A suture withstands stress in one direction only. Therefore, if composite tissues are used they must necessarily be larger than the tissues in which the fibers are parallel. The tendons and the erector spinae muscle have a parallel arrangement of their fibers and have been shown to have approximately the same strength per unit area. Therefore, they would be more uniform than composite tissues.

It is obviously impossible to measure the exact area of cross-section of a transplant before it is inserted. However, if the approximate thickness is known, the width may be estimated, giving a comparative approximation of the area of cross-section. The average thickness of the aponeurosis of the external oblique muscle is 0.2 mm.; that of fascia lata, 0.3 mm., and that of erector spinae muscle, 1 mm. A suture of erector spinae muscle one-fifth or one-third the width of the external oblique muscle and fascia lata, respectively, would possess approximately the same tensile properties. In my opinion, strips of fascia lata should be between 5 and 10 mm. in width, and if greater strength is required, multiple sutures should be used. Sutures of erector spinae muscle between 1 and 2 mm. in width would usually be of sufficient strength for transplantation. These examples are given for comparison only, and the strength and size of sutures should always be considered in relation to the strength of the tissues in which they are embedded and in relation to the clinical stresses to which they will be subjected after transplantation. If a suture is placed in bone, a much heavier one can be used than could be placed in muscle.

The accuracy with which a suture is cut and placed is of even greater importance than its size. A large suture in which shear may develop on application of physiologic stress will be much less effective than a smaller one so prepared and placed as to reduce shear to a minimum. For the same reason, if the suture is traumatized in its handling, removing or placing, intrinsic changes may take place, which on the application of stress will produce the same type of phenomenon shown in figure 9. It might be wise at this point to reiterate that shear and trauma reduce the elastic limit, and on the application of stress such tissues may begin to disintegrate almost immediately. It is safe to

predict that as the clinical work on fascial transplantation progresses, the sutures will be of smaller size than those now used, but much greater attention will be paid to the selection and placing of such tissues.

OTHER FACTORS IN TRANSPLANTATION

The exact amount of any tissue that can be safely removed for transplantation at the present time depends largely on clinical observation. As knowledge concerning the relative strength of these tissues and determinations of a safety factor in body mechanics become available, it will be possible to have definite determinations to guide one in the amount of fibrous tissue that may safely be removed from certain portions of the body. In compensation work, particularly, many claims for disability may arise if too much tissue is removed, especially if an extra incision is made to obtain the transplant. Extra incisions necessarily add to the gravity of any operation, and the choice of method when more involved technic is necessary will depend in all cases on the surgeon.

The research work of Howes¹¹ shows that the tensile properties of prepared sutures decline rapidly after they are embedded in their host tissues, whereas the clinical work of Gallie and LeMesurier¹⁸ and of Bunnell¹⁹ shows that fascial transplants, if properly coaptated, retain their tensile properties indefinitely. A comparison of the physiologic strength of the two materials after transplantation is as yet impossible. The lymphatics are carried to the transplants through fibroplasia. The active rôle of the living suture transplant is in sharp contradiction to the passive rôle of the prepared suture. If the sutures are of excessive size or are rolled on themselves, their central portions may receive an inadequate supply, endangering their viability. The technic must lend itself to much more careful coaptation than for tissues supplied entirely by blood vessels.

No hard and fast rules are as yet justified, so that the selection of cases for transplantation, the determination of the kind of tissues to use and the size of the transplant must for the present at least be left to the clinical judgment of the surgeon. In each case there are many factors which will cause variation, and a few determinations of these are now available, although the few that have already been made have proved themselves invaluable.

ELASTICITY AND TENSION OF FIBROUS TISSUE

By referring to the summary in figures 3 and 4, included in the data, one will find that the entire group of fibrous tissues studied possess a relatively high elasticity. Individual variations are included in the

graphs for the respective tissues. The normal physiologic range of elasticity was maintained to a minimum stress of 500 Kg. per square centimeter.

On the basis of the original concepts of form in relation to function, little doubt can exist that the high elasticity of these tissues is a functional adaptation to maintain properly tonus and contour in fascial structures and to transmit power between the component members of the locomotor group. In the same way that the spinal column has the dual function of supporting the body and protecting the spinal cord, the fascial fibers have the dual function of supporting various structures and protecting the nerves and blood vessels in their course to the periphery. It is also logical to expect that these functions will be performed with an adequate factor of safety.

Such properties doubtless exist in a relative degree in tissues in which there is a smaller percentage of fibrous elements. The ideal application of these principles surgically would be to transplant fibrous tissues so that they could withstand stress closely approximating the normal physiologic range of elasticity and at the same time the viability of the transplant would not be endangered.

Determinations of elasticity during testing were available only when the tissues were held firmly in the clamps and when shear and trauma to these tissues had been eliminated. A parallel may be drawn in surgical technic. The transplant must be firmly anchored in its host tissue and so placed that physiologic stresses may be withstood with a minimum of shear. Variations in this procedure will produce intrinsic changes in the transplant.

A discussion of elasticity inevitably leads to discussion of the optimum tension of the transplant. Unfortunately, at present no determinations of normal tension are available. This statement is made with due deference to the work of Mayer²¹ and after extensive personal experimentation. One should, therefore, endeavor to transplant living tissues at a tension approximating that of the normal tissue. Fascial transplantations permit insertion under tension, whereas prepared sutures seldom adapt themselves to this technic.

FAILURES IN TRANSPLANTATION

The successful transplantation may be regarded as one in which the process of repair, including the process of adaptation, results in complete return of physiologic function in a minimum time. Delayed convalescence could be caused by factors which would delay the process of repair, but the process of adaptation eventually results in a partial or complete resumption of function. Some of the more frequent causes of failure in transplantation may be briefly considered: (1) infection, (2) atrophy of the transplant and (3) death of the transplant.

It is not within the scope of this work to stress fully the importance of rigid preparation of the skin and a strict aseptic technic. In a personal communication from a well known surgeon who has had vast experience in the living suture repair of hernia it was stated that the percentage of infections associated with such repair was higher than in similar cases in which other suture material was used.

If the technic involves two incisions and the operation is unduly prolonged, the liability of infection is increased. The number of assistants required is usually greater, which may be regarded as another possible source of infection. Until the operating teams have performed a number of these operations, they will not work with the same coordination as when they are doing more or less routine work.

Atrophy of the transplant should be considered as a result of factors which so interfere with the process of adaptation that portions of the transplant are no longer of physiologic value. Thus the process of repair ceases, and the process of involution begins. The portions which are no longer of physiologic value will tend to be extruded. In my opinion this accounts for the serous discharge noted by many surgeons. If the process of involution is not sufficient to take care of such tissue adequately the entire transplant may die and be extruded. It should be mentioned, however, that the fibroplasia which has formed around the transplant in certain cases will be of sufficient strength to give a satisfactory result eventually. The surgeon, therefore, should not be in any haste to remove a transplant at the first sign of infection, but should rather give nature every chance to make a satisfactory repair. The process of repair will in many cases be more effective than surgical intervention in an infected field.

On what would a technic be based which would avoid the common causes of failure and at the same time incorporate the salient features of the physical properties here portrayed?

TRAUMA AND ATRAUMATIC TECHNIC

The graphic presentation of the effect of trauma (fig. 9) on fibrous tissue shows the rôle that trauma plays in weakening these tissues. The atraumatic technic of Bunnell deserves special attention.

If prepared sutures are used, trauma occurs only in the tissues in which such sutures are embedded. In transplantation of fibrous tissue, however, trauma may result in injury to the transplant, to tissues from which it is removed and to the host tissue. The technic,³⁴ therefore, should minimize the amount of trauma in each of these three fields.

34. Gratz, C. M.: Use of Fasciae in Reconstructive Surgery, *Ann. Surg.* 99:241-245, 1934.

Incision of the skin and superficial tissues should, if possible, parallel the direction of the fibers of the transplant. Adipose tissue should be removed by sharp dissection rather than by blunt dissection or gauze. The transplant should be cut in the exact direction of its fibers and should be removed by sharp dissection to minimize trauma. The various types of fascial strippers now used may often unnecessarily traumatize the transplant. Some surgeons tear the transplant instead of dissecting it cleanly. This procedure should be condemned.

After the transplant has been removed, it should be kept in gauze moistened with saline or Ringer's solution, and no effort should be made to test its strength, as this may cause intrinsic changes. Unnecessary trauma is caused to the tissue around the transplant by inadequate incisions and excessive traction. The practice of allowing the junior members of the operating team to remove the transplant should be avoided.

It is frequently difficult to place the transplant satisfactorily in the host tissue. This is particularly the case when it is placed in rather remote osseous positions. Special instruments³⁵ have been devised by me for reducing the amount of trauma in inserting these sutures. Certain parts of the transplant will necessarily be traumatized, especially where clamps and needles are applied. This can be lessened by fastening the instruments only once and by not changing their fixed positions. When the sutures have been fastened in place, the traumatized areas should be removed. Since this minor point has been incorporated in the technic, serous discharge has been materially lessened.

TECHNIC TO REDUCE SHEAR PHENOMENA

This discussion will be limited to the transplantation of living suture, but all surgical procedures should be devised so as to reduce shear phenomena to a minimum.

Cutting fibrous tissues transversely necessarily causes more shear when these tissues heal than when such incisions are made parallel to the direction of the fibers. If the physiologic stress after transplantation is borne in part by the transplant and in part by the prepared sutures, the prepared sutures will necessarily produce shear. The entire post-operative stress should be borne by the transplant itself, and the fibers of the transplant should be parallel to the direction of such forces.

Practically this has been found to be easily accomplished by tying the living sutures in a square knot, preventing its slipping by small absorbable sutures, and then fastening both sides of the knot securely to fibrous tissues surrounding it. When stress is applied, the living

35. Gratz, C. M.: New Instruments for Living Sutures, *Am. J. Surg.* **13**:81-82, 1931.

sutures alone carry it. If large sutures are used the physiologic stresses will rarely all be evenly applied, hence a shear phenomenon will result. This can be markedly minimized by using several small sutures rather than one or two large ones. Any technic involving rolling the suture on itself or twisting it will cause shear.

In the absence of any definite determinations of tension, one should strive to place these sutures under a tension similar to that found in normal tissues. This technic will permit the suture to bear a normal amount of stress and will also permit it to resume its normal elasticity rapidly. The strength of internal fixation is thereby increased and the period of convalescence is accordingly diminished.

COMMENT

The clinical applications of these findings to autogenous transplantation have been indicated. In the words of Hawley,⁹ the research work done has been clinically applied to explain "why the transplantation of mesoblastic tissue is successful in some instances and a failure in others." In addition, the clinical application of studies of shear phenomena explains why "those cut on the shear and those cut precisely in the axis of the long fibers look alike, but the former are practically useless for the biological purpose." The salient features of a technic applying these principles have been referred to and have been shown by moving pictures. Reference has been made to the various clinical procedures that have been published over a period of many years coordinating the clinical application of the principles enunciated. A sufficiently large clinical follow-up study has shown that these principles are physiologically sound.

The unpublished work of Prentiss, of Iowa State University, and the clinical application of his work by Milgram³⁶ to the surgical treatment of suppuration in the fascial spaces of the thigh are outstanding contributions to fascial surgery. The recent book of Singer on the anatomy of fasciae supplies a long felt need. No work on fascial surgery would be complete without due reference to the splendid research and clinical work of Koontz³⁷ in his use of prepared fasciae as transplants.

The fasciae of animals are functionally designed for the transmission of stress and strain and hence should be more suitable for suture material than catgut, the primary function of which is digestion. When various problems in preparing, sterilizing and placing prepared fascial

36. Milgram, J. E.: *Surgery of Suppuration in the Fascial Spaces of the Thigh*, J. A. M. A. **98**:117-123 (Jan. 9) 1932.

37. Koontz, A. R.: *Muscle and Fascia Suture with Relation to Hernia Repair*, Surg., Gynec. & Obst. **42**:222-227, 1926.

sutures have been completed, such sutures should have a large field of usefulness. It may, however, be in order to suggest that when the entire body is available for the removing of sutures, the various tendons and the fasciae of the back might prove more suitable than fascia lata. The present ox fascia lata commercially supplied could be readily improved by cutting the suture along the direction of their fibers and thus reducing shearing stress. While it is believed that autogenous fibrous tissues are theoretically the ideal suture material it is realized and hoped that their field of usefulness will always be limited to selected cases, whereas prepared fibrous sutures have theoretically a much larger field. The similarity between the biomechanical properties of tendons and fasciae has been shown throughout this entire work. This was confirmed by histologic studies and the findings correlated with the clinical application. The mesothelial covering of the fascial planes requires the development of a physiologic technic for operations on fasciae paralleling the physiologic technic of Mayer,³⁸ which he developed for operations on tendons. Linking the studies, however, with functional anatomy, operations on the fasciae may be of even greater importance in relation to pain and limitation of motion than operations on the tendons. The fact that the nerves, blood vessels and lymphatics traverse the fascial spaces and are in intimate contact with the mesothelial covering of these spaces makes them of the greatest surgical importance.

With these physiologic conceptions applied to operation on the fasciae, it is of interest to study operative procedures developed for the relief of symptoms in pain low in the back and sciatica.

Percy Roberts did a large number of cutting operations on the fasciae many years ago, though he did not publish the results of his work. Heyman³⁹ has done a similar type of operation, but it was the work of Ober³⁹ that has focused the attention of the surgical world on the possible rôle of the soft tissue in the syndrome of sciatic pain low in the back. Ober's³⁹ procedure, the dividing of the tensor fascia lata, has been widely employed by clinicians of the highest standing, and all have reported a goodly percentage of favorable results from this procedure. Nevertheless, the rationale of the operation with relation to the etiology of the pain has never been sufficiently clarified.

Manipulations of various sorts, but all fundamentally aimed at relief of pain, whether on the lumbosacral or the sacro-iliac joint, and the more recent operations on the soft tissue have all been credited with

38. Heyman, C. H.: Thoughts on the Relief of Sciatic Pain, *J. Bone & Joint Surg.* **16**:889 (Oct.) 1934.

39. Ober, Frank R.: The Role of the Iliotibial Band and Fascia Lata as a Factor in the Causation of Low Back Disabilities and Sciatica, *J. Bone & Joint Surg.* **18**:105-110, 1936.

a high percentage of good results. All these procedures, however, have one common factor; viz., the fibrous tissues are either stretched or divided in the course of treatment. If I may be permitted to speculate a bit, it may be deduced from the intimate anatomic relation which the fascial planes bear to the nerves that the relief of pain following these procedures may have been the result of the elimination of tensions on the nerve trunks lying in these tissues, produced by adhesions of the mesothelial covering of the fascial planes at points where there should be motion. Certain patients after manipulation have aggravation of the symptoms rather than relief. It is conceivable that in those patients who have been relieved the fascial adhesions to the nerve were divided by the manipulative forces, whereas in the cases in which the results were unsuccessful the adhesions did not give way but instead injured the nerves or the blood vessels when put on the stretch during the treatment.

Albee's ⁴⁰ work on myofascitis, particularly the toxic involvement of these tissues, would also be confirmed not only by the histology but by the variations in the fascial planes noted by roentgenographic studies. The limitation of straight leg raising noted by him would probably be explained by toxic conditions in the fasciae with resulting fascial adhesions and contractures.

The present work with pneumofasciagrams has not solved the problem of pain low in the back, but the correlation of the entire work may be of aid in localizing the pathologic process in these cases. The therapeutic action of treatment of the fascial spaces alone is of decided clinical interest, but an adequate follow-up is necessary before conclusions can be drawn, and the utmost conservatism is being used.

This work has been developed, and the results have been of interest to many groups other than surgeons. The members of the department of pharmacology at Columbia University were particularly interested in the establishment of normal biomechanical determinations in anticipation of comparing these with similar studies in cases in which there was a disturbance of calcium metabolism. The research workers from the Bell Laboratories were also hopeful of using the normal determinations of fasciae as an aid in the study of changes of the fibrous tissues in the human ear. Plans for biomechanical studies of pulmonary adhesions have been made by clinicians studying tuberculosis. Members of the engineering and architectural professions have cooperated throughout and have been interested not only in the remarkable physical properties of the fibers of the fascial planes but also in the coordination of soft tissue movement which takes place through the fascial planes. Roentgenologists have aided in developing the technic for visualizing the fascial planes, using air as a contrast medium.

40. Albee, Fred H.: Myo-Fascitis, *Am. J. Surg.* **23**:70-78, 1934.

SUMMARY

Certain physiologic properties of the fibrous tissues from a cross-section of mammals are presented in engineering units of tensile strength and elasticity. Determinations of the proportional limit of these tissues are presented and the elasticity is measured in terms of Young's modulus. The proportional limit of biologic material is regarded as a measure of the physiologic range of elasticity and probably indicates the dividing line between stress which causes no permanent damage to fibrous tissues and stress which causes intrinsic changes and permanent impairment of function.

The similarity between species makes such determinations pertinent to man; the similarity between tendons and fasciae makes a large proportion of the research and clinical work on tendons pertinent to operations involving the fasciae. The consistency of the results of all determinations on normal adults probably indicates that the variation in weight in the individual animals is compensated for by the variation in size in the individual structures.

The studies of fibrous tissues herewith presented after normal growth and the research and clinical work herewith reviewed in relation to fibroplasia after surgical repair and transplantation show definite adaptations of form to function.

Shearing stress and trauma markedly diminish the physical properties studied, and their effect is graphically portrayed. These findings are clinically applied to devise a physiologic technic of fascial transplantation. The facts given permit the presentation of definite principles to guide one in the selection of cases and the selection of tissues suitable for fascial transplantation.

Brief reference is made to other fields in which these findings are of value. Particular reference is made to the rôle of the fascial planes in the mechanics of the soft tissues of the locomotor apparatus. The functional mechanics of the soft structures are considered in relation to the rôle of fascial adhesions in pain low in the back. Brief reference is made to the normal mesothelial covering of the fasciae and changes in these tissues in pain low in the back and arthritis. It is believed that chronic infective processes may be as closely associated with the fascial spaces as Kanavel has shown acute infections to be.

Dr. S. N. Blackberg, of the Department of Pharmacology of Columbia University; Prof. G. B. Karelitz, of the Department of Mechanical Engineering of Columbia University, and R. L. Wegel, of the Bell Laboratories, checked the work reported here during preparation and carefully reviewed it.

SIGNIFICANCE OF THE OBSTRUCTIVE FACTOR IN THE GENESIS OF ACUTE APPENDICITIS

AN EXPERIMENTAL STUDY

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AND

WARNER F. BOWERS, M.D.

MINNEAPOLIS

The significant rôle of the vermiform appendix in the causation of perityphilitic suppuration was established by Fitz,¹ of Boston, in 1886. This was almost fifty years ago, and in the intervening years, thanks to the fruitful labors of Pasteur and Lister, surgery has broadened in its scope from a science concerned primarily with the dressing of wounds to one holding an important position in the treatment of disease. Knowledge concerning the recognition of the clinical picture of appendicitis and the surgical technicalities involved in its removal have grown apace, but information concerning the nature of the origin of appendicitis remains almost as obscure as when Fitz made his prophetic pronouncement.

Appendicitis continues to prove fatal, and if one considers actuarial tabulations, the mortality is increasing. In the last twenty-five years² there has been an increase of 30 per cent. Whether this is apparent or real is not yet wholly evident, but it is obvious that the accomplishment of the surgeon in dealing with acute appendicitis has not kept stride with his potential capacity of coping with the problem. The supreme misfortune which can befall a man, said Leonardo de Vinci, is that theory outstrips performance.

How this record can be best improved is not immediately clear. A common human failing of overhopeful optimism and too frequent practice of the policy of "wait and see" by both the patient and the

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Read at the meeting of the Western Surgical Association, Rochester, Minn., Dec. 6, 1935.

1. Fitz, R. H.: Perforating Inflammation of the Vermiform Appendix with Especial Reference to Its Early Diagnosis and Treatment, *Am. J. M. Sc.* **92**:321, 1886.

2. Hoffman, F. L.: Appendicitis Record of 1934, *Spectator (Life Ed.)* **135**: 6, 1935. Wilkie, D. P. D.: Observations on Mortality in Acute Appendicitis, *Brit. M. J.* **1**:253, 1931.

physician probably account in a large measure for the unwarranted number of deaths from a malady which if treated intelligently and opportunely would command no great hazard to life. The confused present state of medical opinion concerning the causative factors of appendicitis undoubtedly contributes in no small measure to this somewhat humiliating achievement with the problem of appendicitis. Whereas a disease process may frequently be treated fairly successfully in an empirical fashion, an adequate appraisal of the nature of the disease invariably, in the better understanding, lends a tremendous impetus to the correction of defects in its management.

PRESENT CONCEPTS OF THE ORIGIN OF APPENDICITIS

The chaotic condition of knowledge with reference to the etiology of appendicitis may readily be discovered by perusal of a few of the numerous papers in the literature which profess to bring enlightenment into this disordered state. One gains the impression from studies made with reference to the geographic distribution of appendicitis³ that in the main it is a disease of civilization and culture, in which diet and lack of physical activity are the chief determinants. How much credence one may with confidence give these general observations is a pertinent query. The physician learns from experience that as the vagaries of a disease process are more familiar, the condition seems to be encountered more often. There is, moreover, no reliable information to indicate that the disease actually is more frequent in countries where it may be properly identified than it was before it was recognized.

In the diet, the following have been alleged to be of some importance in predisposing to the occurrence of appendicitis:⁴ food preservatives, enamel ware employed in cooking, the extensive eating of frozen and preserved meat, bananas, increased consumption of sugar, iron from the iron rollers employed to grind grains into flour and cereals and an inadequate amount of cellulose. These and a large number of other dietary items have been held accountable for the frequency of appendicitis among civilized people.

Among exciting causes, infection and obstruction are commonly acknowledged as being likely etiologic agencies. Those who admit the obstructive element contend that it probably accounts for only a minority of the cases. The factor of infection, then, is generally conceded as playing the dominant rôle in the production of acute appendicitis. In what manner the infection reaches the appendix, even among those

3. Murray, R. W.: The Geographical Distribution of Appendicitis, *Lancet* 2:2227, 1914.

4. Short, A. R.: The Causation of Appendicitis. *Brit. J. Surg* 8:171, 1920.

who maintain that appendicitis is solely a bacterial disease, is not a matter of agreement. Adrian⁵ and Kretz⁶ hold that the disease is blood borne, usually from an infection of the throat and tonsils. Poynton and Paine⁷ and Rosenow⁸ by inoculation of animals have brought forth experimental data to support this belief, and such an opinion is wholeheartedly shared by a large number of surgeons and practitioners. Aschoff,⁹ who gave the problem considerable thoughtful and critical study, maintained, on the contrary, that the infection arises in the majority of instances from within the bowel. In a recent monograph on the subject,^{9c} he set forth the opinion that appendicitis is probably a specific bacterial disease, like gonorrhea; that the causative agent, an enterococcus, more specifically a type of streptococcus, corresponding to Gundel's¹⁰ enterococcus type.B, which Aschoff described as a gram-positive diplococcus, normally resides in the distal third of the appendix and under proper conditions becomes pathogenic and gives rise to the pathologic picture of appendical suppuration.

In normal appendixes, Aschoff has found a flora of organisms which is not unlike that of the cecum, consisting of streptococci, colon bacilli and gram-positive rods in the proximal two thirds of the appendix in from 62 to 70 per cent of instances. In the distal third, however, diplococci are found as the sole or predominant organism in the majority of instances. In acute suppuration of the appendix, Aschoff has found diplococci in pure culture in 65 per cent of instances, and when the allied enterococci and nonhemolytic streptococci are included, these organisms are accountable for more than 70 per cent of instances of

5. Adrian, C.: Die Appendicitis als Folge einer Allgemeinerkrankung—Klinischer und Experimentelles, Mitt. a. d. Grenzgeb. d. Med. u. Chir. **7**:407, 1901.

6. Kretz, R.: Untersuchungen über die Aetiologie der Appendicitis, Mitt. a. d. Grenzgeb. d. Med. u. Chir. **17**:1, 1907.

7. Poynton, F. J., and Paine, A.: Experimental Appendicitis by General Blood Stream Infection, Tr. M. Soc. London **35**:243, 1912; Lancet **2**:439, 1912.

8. Rosenow, E. C.: The Bacteriology of Appendicitis and Its Production by Intravenous Injection of Streptococci and Colon Bacilli, J. Infect. Dis. **16**:240, 1915; Focal Infection and Elective Localization of Bacteria in Appendicitis, Ulcer of the Stomach, Cholecystitis, and Pancreatitis, Surg., Gynec. & Obst. **33**:19, 1921.

9. Aschoff, L.: (a) Ueber die Bedeutung des Kotsteines in der Aetiologie der Epityphlitis, Med. Klin. **24**:587, 1905; (b) Die Wurmfortsatzentzündung, Jena, Gustav Fischer, 1908; (c) Appendicitis: Its Etiology and Pathogenesis, London, Constable & Co., Ltd., 1931.

10. Gundel, M.: Ueber die "Erregerfrage" bei der Appendicitis im post-appendicularen Peritonitis, Arch. f. klin. Chir. **172**:597, 1933. Gundel, M.; Pagel, W., and Sussbrich, F.: Untersuchungen zur Aetiologie der Appendicitis und post-appendiculären Peritonitis, Beitr. z. path. Anat. u. z. allg. Path. **91**:399, 1933.

acute appendicitis. Moreover, Aschoff¹¹ stated that these organisms are the likely pathogenic agents in probably 100 per cent of the cases.

A large number of investigators share in part the view expressed by Aschoff, i. e., that inflammation of the appendix arises locally from the bowel and is not blood borne. The greater number of these, however, believe that a number of organisms may cause suppuration in the appendix and that the infection is brought to the appendix by way of the proximal portion of the intestinal canal. Hilgermann and Pohl¹² find in suppurative appendicitis the same organisms, in the main, as may be found on culture of material from the throat in tonsillitis, viz., pneumococci, streptococci, diphtheroid bacilli and Vincent's organisms. They expressed the belief that these organisms are swallowed, find their way into the appendix and set up in the submucosal lymphoid tissue the same type of inflammation as they cause in the tonsil. Warren,¹³ in a combined histologic and bacteriologic study, concluded, on what appears to be good evidence, that a variety of organisms may give rise to suppurative appendicitis.

EXPERIMENTAL INVESTIGATION

PURPOSE

The thought which is frequently in the surgeon's mind concerning the appendix is that it is essentially a long, narrow diverticulum of the cecum with an arrangement unfavorable for ready and complete evacuation of its content. Specific infection in the alimentary canal is so unusual as to suggest that the anatomic plan of the vermiform appendix may be largely responsible for the frequency with which appendicitis occurs in man. With this consideration as a premise, we have tried to evaluate the significance of the obstructive factor in the genesis of appendicitis by experiments on animals and by careful observation of the frequency with which obstructive phenomena are noted in the spontaneous occurrence of the disease in man.

CHOICE OF ANIMAL AND ANATOMIC CONSIDERATIONS

The vermiform appendix of man represents the true apex of the cecum. One of the characteristics of the cecal apex which the human appendix exhibits in liberal measure after the first few weeks of life

11 Aschoff, *loc. cit.* pp 68 and 69

12 Hilgermann, R., and Pohl, W. Beitrag zur Aetiologie und Serum Therapie der foudroyanten Appendicitis auf Grund der Beobachtungen bei 300 Fallen im Kreis Deutsch-Krone, *Arch f klin Chir* **154**:248, 1929

13 Warren, Shields. Etiology of Appendicitis, *Am J Path* **1**:241, 1925

is a large amount of lymphoid tissue.¹⁴ Not many mammals besides man possess a true vermiform appendix. Of the common laboratory animals, the rabbit is the only one which does. Its appendix is a real lymph gland, in which the chief distinguishing feature is the extremely abundant lymphoid tissue. The wombat, the lemur and the higher anthropoid apes possess a true vermiform appendix. The spontaneous occurrence of appendicitis in the chimpanzee has been recorded. Weinberg found evidence of acute suppurative appendicitis in ten of sixty-one chimpanzees dying in captivity. He has also reported its occurrence in a gorilla and accompanied his report by well supported proof in appended illustrations. Murray stated that Plummer observed the spontaneous occurrence of appendicitis in three higher apes (one chimpanzee

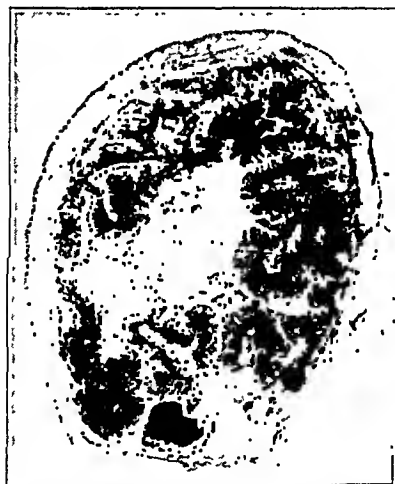


Fig. 1.—Photomicrograph of a normal dog's cecal appendage.

and two gibbons) at the London Zoo. He also observed inflammation of the cecal apex in fifteen wild animals of various kinds dying in captivity. Dr. Hamerton, pathologist of the Zoological Society of London, recently wrote us that only two instances of appendicitis have been observed there in the subhuman primate family in the last twenty years. Both occurred in gibbons. The director of the Zoological Gardens in Berlin wrote us that a single instance of appendical abscess had been observed there, in a 10 year old gorilla.

In this study the dog, in which the cecum is an appendage to the colon, was largely used. A lesser number of experiments were also done on rabbits. True, the dog does not have a true vermiform appen-

14. Berry, R. J. A., and Lack, L. A. H.: The Vermiform Appendix of Man and the Structural Changes Therein Coincident with Age, *J. Anat. & Physiol.* **40**: 247, 1905.

dix, but as the appendix and the cecal apex are comparable structures, it was felt that no apology need be offered in employing the cecal appendage of the dog. In this study, extending over two years, one hundred and thirty-nine experiments were done on dogs and ten on rabbits (fig. 1).

MODE OF STUDY

The greater portion of this experimental inquiry concerns itself with the factors of obstruction and infection. In addition, a lesser number of experiments have been done in which the blood supply to the appendix was interfered with, and finally a miscellaneous group of somewhat unrelated experiments were done with a view to a better interpretation of the preceding experiments.

The essential approaches to the problem employed in this experimental inquiry are as follows: (1) establishment of obstruction—complete and incomplete—to the cecal apex with and without washing of the lumen; the employment of peritoneal exudates; the maintenance of sustained intraluminal pressure, and the isolation of the cecal appendage as a closed loop; (2) determination of the rôle of infection with relation to the absence of obstruction, the presence of partial and complete obstruction, the significance of the specificity of organisms and embolic systemic infection; (3) interference with the circulation of the cecal apex; (4) traumatization of the wall; transplantation of the vascularized cecal apex to other segments of the intestinal canal; the injection of phenol into the lumen and of exudate, organisms and melted paraffin into the wall of the cecal apex.

All operations were done under the usual aseptic precautions. No animal was starved longer than twelve hours before operation. Pentobarbital sodium (35 mg. per kilogram of body weight) was given intraperitoneally for anesthesia. In the experiments in which continuous increased intraluminal pressure was maintained over a considerable period, this anesthesia was supplemented by the use of morphine.

The cecal appendage was excised under sterile technic at varying intervals of time after the performance of the procedures outlined. In the majority of instances the results of the examination of tissues here reported concerned living dogs. Animals dead for several hours at the time of postmortem examination were discarded from consideration. The excised tissues were fixed in a diluted solution of formaldehyde U. S. P. (1:10) for twenty-four hours, after which representative blocks were cut. These blocks were embedded in paraffin and stained with hematoxylin and eosin for histologic examination, and in the greater number of instances the Gram-Weigert stain was used as well for purposes of studying the bacteria. In the majority of cases smears and cultures were made from the lumen and wall of the cecal apex for identification of the bacteria present.

CRITERIA OF DIAGNOSIS

In each instance the gross features were carefully noted. Hemorrhage, gangrene, perforation, thickening and thinning of the wall and suppuration represent the variety of macroscopic pathologic changes noted. A diagnosis of acute inflammatory change was made only in cases in which microscopic evidence of edema, hemorrhage and leukocytic infiltration of the wall of the bowel, predominantly of the poly-

morphonuclear variety, were demonstrable. Such changes limited to the serosa were considered the result of operative trauma. Mild acute appendicitis was diagnosed in the presence of minimal diffuse reaction; moderately severe acute appendicitis, in the presence of moderate reaction, and gangrenous appendicitis, in the presence of severe hemorrhage with evidence of tissue necrosis (fig. 2).

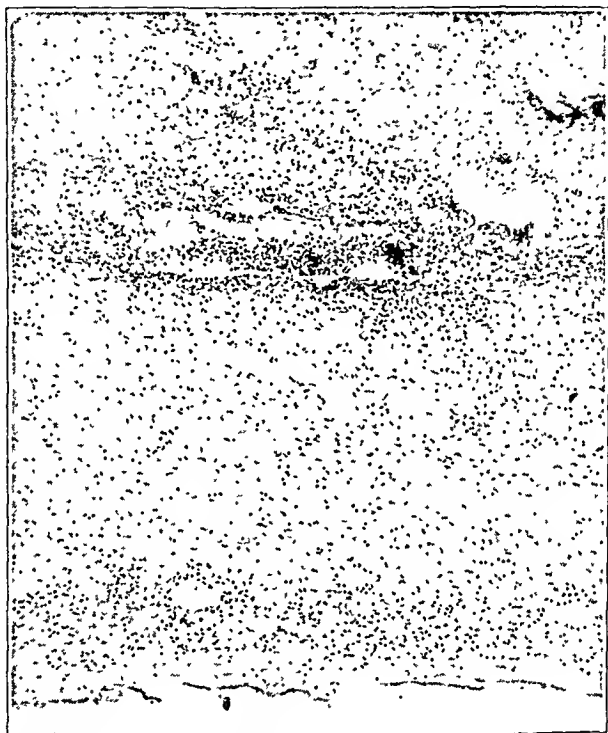


Fig. 2.—Photomicrograph indicating the marked serosal edema and leukocytic infiltration characteristic of the sections in the experimental series on which a diagnosis of acute appendicitis was made. The section was taken from dog 130 after maintenance of 8 cm. of constant water pressure for six hours.

RESULTS OF EXPERIMENTS OBSTRUCTION

COMPLETE OBSTRUCTION.—*Complete. Obstruction of the Lumen of the Cecal Appendage by a Ligature at the Base.*—There were eight dogs in this series, in which complete obstruction of the lumen of the cecal appendage was produced by ligature at the base with heavy linen thread. In three dogs the cecal appendage was excised after six hours of obstruction; in three, after eighteen hours, and in two, after twenty-four hours. After six hours of obstruction one cecal appendage was normal, one was definitely acutely inflamed and four were gangrenous. After eighteen hours, one was normal, and the other two were gangrenous. After twenty-four hours one showed definite evidence of acute inflammation, while the other was gangrenous. In each case in which the appendix was normal it was found to be

firmly contracted down, whereas the acutely inflamed and gangrenous specimens were tensely distended with a hemorrhagic fluid. Smears of this fluid from each cecal appendage usually showed an abundance of leukocytes and a wide variety of organisms, including *B. coli*, *B. Welchii*, and gram-positive and gram-negative streptococci. In one instance many gram-positive diplococci were seen within the leukocytes (table 1).

TABLE 1.—*Result of Complete Obstruction of the Cecal Appendage by Ligature*

Dog No.	Time, Hr.	Gross Description	Bacteriologic Picture	Diagnosis
1	6	Much bloody peritoneal fluid; cecal appendage gangrenous and tensely distended with fluid	Gram positive rods, diplococci, diplobacilli and streptococci; very sparse gram negative diplococci	Acute gangrenous appendicitis
2	6	Much bloody peritoneal fluid; cecal appendage moderately congested	Normal
41	6	Moderate peritoneal fluid; cecal appendage congested and distended	Gram-positive diplococci; gram negative rods and diplococci	Early acute appendicitis
5	18	Much foul peritoneal fluid; cecal appendage gangrenous and tensely distended with fluid	Gram-positive streptococci, rods and large bacilli	Acute gangrenous appendicitis
6	18	No peritoneal fluid; cecal appendage grossly normal	Normal
42	18	Moderate peritoneal fluid; cecal appendage gangrenous in two areas and tense; contents foul and bloody	Phagocytosis of gram positive diplococci; gram positive rods, diplobacilli, streptococci and diplococci; gram negative bacilli, streptococci and diplococci	Acute gangrenous appendicitis
7	24	Cecal appendage gangrenous and tensely distended with fluid	Many leukocytes; sparse gram negative streptococci and diplococci	Acute gangrenous appendicitis
8	24	Moderate bloody peritoneal fluid; cecal appendage congested	Gram positive diplococci	Acute appendicitis

TABLE 2.—*Result of Complete Obstruction of the Cecal Appendage and Introduction of Virulent Peritoneal Exudate in the Lumen*

Dog No.	Time, Hr.	Gross Description	Bacteriologic Picture	Diagnosis
27	24	Much foul bloody peritoneal fluid; cecal appendage completely gangrenous, many perforations	Phagocytosis of gram positive diplococci; gram positive rods, diplococci and streptococci, gram negative rods, diplococci, streptococci	Acute gangrenous appendicitis
28	24	Cecal appendage grossly normal except for moderate edema	Acute appendicitis

Ligature of the Cecal Appendage at the Base and Introduction of Virulent Peritoneal Exudate into the Lumen—In two dogs a small gelatin capsule containing virulent peritoneal exudate from a dog dying of peritonitis from rupture of an obstructed cecal appendage (cultures showed real type of flora) was introduced into the cecum and maneuvered into the cecal apex, which was then obstructed at its base for twenty-four hours. In both instances the cecal appendage showed acute changes, one being gangrenous. Phagocytosis of gram-positive diplococci was again noted in the fluid. The changes in these tissues were more severe than in the previous experiments, and the gangrenous cecal appendage exhibited many perforations (table 2).

Ligature of the Cecal Appendage at the Base and Injection of Melted Paraffin into the Wall of the Cecum Distal to the Ligature.—In two dogs melted paraffin was injected into the wall just beyond the obstructing ligature. One dog died of generalized peritonitis in twenty-four hours, from pressure necrosis and perforation at the site of injection. In the other the cecal appendage was excised in seventy-two hours; necrosis was present in the area in which the injection was made, with milder acute changes demonstrable elsewhere (table 3).

Ligature of the Cecal Appendage at the Base After Washing the Lumen.—This group is composed of three dogs; the cecal appendages were thoroughly washed out with 100 cc. of tap water, a large glass syringe and fine needle being used, followed by ligature at the base. In two dogs the cecal appendage was removed

TABLE 3.—*Result of Complete Obstruction of the Cecal Appendage and Submucosal Injection of Melted Paraffin*

Dog No.	Time, Hr.	Gross Description	Bacteriologic Picture	Diagnosis
31	72	Generalized peritonitis and abscesses; base of cecal appendage necrotic; pus in lumen	Acute appendicitis
32	24	Died of peritonitis due to gas formation; cecal appendage showed peritonitis	Gram-positive large bacilli, diplococci and streptococci rare gram-negative streptococci and bacilli	Serositis

TABLE 4.—*Result of Complete Obstruction of Empty, Washed Cecal Appendage*

Dog No.	Time, Hr.	Gross Description	Bacteriologic Picture	Diagnosis
15	96	No fluid; cecal appendage contracted and grossly normal; omentum adherent; small inspissated fecal mass	Very sparse organisms; gram-positive diplococci, streptococci and spore-forming bacilli; rare gram-negative diplococci and streptococci	Normal
16	96	No fluid; cecal appendage contracted and grossly normal; omentum adherent; small inspissated mass in lumen	Very sparse organisms; gram-positive diplococci, streptococci and spore-forming bacilli; rare gram-negative diplococci and streptococci	Normal
53	120	Died of diffuse abscesses of lung; peritoneal cavity normal except for postmortem changes	Normal

in ninety-six hours and in the other after five days. In no instance was evidence of inflammation noted in the sections; the cecal appendage in each instance was considerably contracted. It should be noted that the factor of distention was absent, although smears from the lumen showed the usual fecal organisms (table 4).

Ligature of the Cecal Appendage at the Base After Washing the Lumen; Release of the Ligature After Some Time; Placement of Feces in the Lumen; Ligature at the Base.—In three dogs the cecal appendage was washed and obstructed for five days. When the second laparotomy was performed the cecal appendages appeared grossly normal. They were then filled with fecal material and reobstructed. One animal died of pulmonary aspiration within six hours. There were petechial hemorrhages over the surface of the cecal appendage, and sections showed early acute inflammatory changes. In one dog the cecal appendage

was removed six days later and was found to be normal, but the obstructing ligature had cut through the tissues and the lumen had become reestablished. The third animal showed acute inflammation of the cecal appendage when it was removed on the seventh day, but the lumen was not distended, and the process was apparently subsiding (table 5).

INCOMPLETE OBSTRUCTION.—*Stenosis of the Appendical Lumen by Ligature of Cecal Appendage at the Base.*—In three dogs stenosis of the lumen was established for seventy-two hours. In one the cecal appendage showed mild acute changes,

TABLE 5.—*Result of Complete Obstruction of Empty Washed Cecal Appendage, Introduction of Feces After Five Days and Reobstruction*

Dog No.	Time, Hr.	Gross Description	Bacteriologic Picture	Diagnosis
33	108	Many adhesions and small abscesses; cecal appendage contracted and walled off; small inspissated mass in lumen	Gram-positive diplococci; gram-negative rods, diplococci and streptococci	Acute appendicitis
34	6	Died of aspiration; cecal appendage distended, walls congested and covered by petechiae	Early acute appendicitis
52	144	Cecal appendage grossly normal; ligature had cut through and lumen partially reestablished; marked stenosis	Gram-positive diplococci; gram-negative rods and diplococci	Normal

TABLE 6.—*Result of Stenosis of the Cecal Appendage by Ligature*

Dog No.	Time, Hr.	Gross Description	Bacteriologic Picture	Diagnosis
9	72	No fluid; cecal appendage grossly normal; slight edema	Early acute appendicitis
10	72	No fluid; grossly normal; fecaliths in lumen	Normal
43	72	Moderate peritoneal fluid; cecal appendage edematous and congested; fecaliths in lumen	Gram-positive rods and diplococci; gram-negative rods, diplococci and streptococci	Normal

TABLE 7.—*Result of Stenosis of the Cecal Appendage Around a Glass Cannula*

Dog No.	Time, Hr.	Gross Description	Diagnosis
11	24	Tube forced through stenosed area and found in rectum; cecal appendage showed moderate congestion	Acute appendicitis
12	24	Cecal appendage edematous and hemorrhagic; fecaliths in lumen	Acute appendicitis

while in the others there was no evidence of inflammation. In all three instances the lumen contained a very inspissated fecal mass, indicating some mechanical dysfunction (table 6).

Placement of a Flanged Tube With a Small Lumen in the Cecal Appendage.—In two dogs stenosis was established around a flanged glass tube introduced through the cecum, with its large end in the apex. The cecal appendage, which was removed in twenty-four hours, exhibited acute inflammation, but it was observed that feces had completely plugged the glass tube, so that in reality a complete obstruction had been present (table 7).

Stenosis and the Introduction of a Foreign Body into the Lumen.—This group comprises eight dogs in which a glass marble was introduced into the cecal apex through the proximal portion of the bowel. The lumen was then stenosed sufficiently by ligature to prevent the escape of the foreign body. The cecal appendages were removed after six, eighteen, twenty-four, fifty-two and seventy-two hours. One of the twenty-four and one of the seventy-two hour specimens showed acute changes and in both of these the marble was tightly pressed against the stenosing ligature by muscular spasm so that a complete obstruction was present. In the other specimens, which were normal, the marbles were found lying free within the lumen of the appendage (table 8).

TABLE 8.—*Result of Stenosis of the Cecal Appendage and Introduction of a Foreign Body in the Lumen*

Dog No.	Time, Hr.	Gross Description	Bacteriologic Picture	Diagnosis
13	6	Moderate peritoneal fluid; cecal appendage grossly normal; had contracted and marble was tight against suture	Gram-positive diplococci, diplobacilli and streptococci; gram-negative cocci, diplococci, bacilli and streptococci	Serositis
114	6	Cecal appendage relaxed and normal	Normal
17	18	Cecal appendage grossly normal; marble tight against ligature; fecaliths in lumen	Serositis
18	18	Moderate peritoneal fluid; cecal appendage relaxed and normal	Normal
19	24	Cecal appendage grossly normal; marble tight against ligature	Early acute appendicitis
20	24	Moderate bloody peritoneal fluid; cecal appendage edematous and showed petechiae; marble tight against ligature; fecaliths in lumen	Serositis
26	52	Generalized gas bacillus infection; postmortem changes	Postmortem necrosis
44	72	Cecal appendage contracted, edematous and showed petechiae; fecaliths	Gram-positive diplococci; gram-negative rods and diplococci	Acute appendicitis

Stenosis and the Introduction of Virulent Peritoneal Exudate into the Lumen.—In four dogs a capsule of virulent peritoneal exudate from a dog dying of peritonitis was introduced into the cecal appendage through the proximal portion of the bowel. Stenosis of the base of the appendage was then produced by means of a ligature. In two animals the appendage was removed after eighteen hours, and in the remaining two, after twenty-four hours. All exhibited a rather severe inflammatory reaction. In some of these edema of the mucosa had produced a complete obstruction (table 9).

Stenosis and the Introduction of a Foreign Body and Virulent Exudate into the Lumen.—In this group nine dogs were used. A capsule of virulent peritoneal exudate was introduced into the appendix through the cecum, and this was followed by the introduction of a glass marble. Stenosis of the base of the cecal appendage was then produced, the marble being proximal to the capsule. In these animals the cecal appendage was removed after eighteen, twenty-four and ninety-six hours and

after seven and nine days. In six instances definite acute inflammation was demonstrable. The animal in which the cecal appendage was removed after nine days was very ill, with nausea and vomiting for four days, and then spontaneously passed the marble by rectum. He showed marked improvement, and his reactions

TABLE 9.—*Result of Stenosis of the Cecal Appendage and Introduction of Virulent Peritoneal Exudate in the Lumen*

Dog No.	Time, Hr.	Gross Description	Bacteriologic Picture	Diagnosis
21	18	Moderate peritoneal fluid; cecal appendage edematous; petechiae	Gram positive diplococci and streptococci; gram negative rods, diplococci and streptococci	Acute appendicitis
22	18	Edema of cecal appendage; petechiae	Gram positive diplococci and streptococci; gram negative rods, diplococci and streptococci	Acute appendicitis
23	24	No fluid; cecal appendage grossly normal but for some edema	Acute appendicitis
23 5	24	Moderate bloody peritoneal fluid; cecal appendage hemorrhagic	.	Acute appendicitis

TABLE 10.—*Result of Stenosis of the Cecal Appendage and Introduction of a Foreign Body and Virulent Peritoneal Exudate into the Lumen*

Dog No.	Time, Hr.	Gross Description	Bacteriologic Picture	Diagnosis
3	18	Moderate peritoneal fluid; edema and petechiae; fecal liths in lumen	..	Acute appendicitis
4	18	Moderate peritoneal fluid; edema and petechiae	. .	Acute appendicitis
24	24	Some bloody peritoneal fluid; edema and petechiae; friable	. .	Acute appendicitis
25	24	Moderate peritoneal fluid; some edema of cecal appendage	Gram positive diplococci, streptococci and rods	Normal
51	24	Moderate peritoneal fluid; edema and petechiae; fecal liths	Gram positive diplococci and rods; gram negative rods and streptococci	Normal
39	96	Cecal appendage hemorrhagic; fecal liths	..	Normal
45	168	Cecal appendage grossly normal	Gram positive diplococci and rods; gram negative diplococci, streptococci and rods	Acute appendicitis
46	168	Cecal appendage edematous; petechiae	Gram positive diplococci, streptococci and rods; gram negative diplococci, streptococci and rods	Acute appendicitis
40	216	Dog very ill 4 days and then passed marble; cecal appendage showed petechiae and edema; fecal liths	Gram positive rods and diplococci; gram negative rods and diplococci	Mild acute appendicitis

were normal by the ninth day. Examination of the specimen showed minimal acute changes, apparently in regression (table 10).

Stenosis and the Injection of Melted Paraffin Submucosally—After stenosis of the lumen of the cecal appendage of two dogs was produced by a ligature, melted paraffin was injected into the submucosa and the specimens were removed after

seventy-two hours. In both instances acute inflammatory changes were present, which were attributed to the hot paraffin (table 11).

MAINTENANCE OF CONSTANT INCREASED INTRALUMINAL PRESSURE.—In the foregoing experiments it was observed that in almost every instance in which an acute inflammatory reaction was induced there had been distention of the lumen by fluid. The following experiments were devised to determine what effect constant increased intraluminal pressure would have on the wall of the cecal appendage of the dog. This group is composed of eighteen dogs, and in each instance a metal cannula was introduced into the lumen of the cecal appendage at its base through an incision

TABLE 11.—*Result of Stenosis of the Cecal Appendage and Submucosal Injection of Melted Paraffin*

Dog No.	Time, Hr.	Gross Description	Bacteriologic Picture	Diagnosis
29	72	Some bloody peritoneal fluid; cecal appendage hemorrhagic and bound down; edema; fecaliths	Acute appendicitis
30	72	Some bloody peritoneal fluid; cecal appendage edematous and congested; pus in lumen	Gram-positive diplococci and streptococci; gram-negative rods, diplococci and streptococci	Acute appendicitis

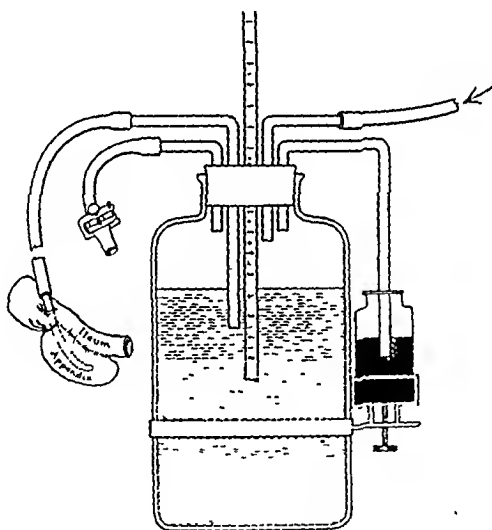


Fig. 3.—A constant pressure apparatus which can be arranged to deliver any desired air or water pressure.

made in the proximal portion of the colon. The base of the cecum was then tied tightly about the cannula, which was attached to a Perusse¹⁵ constant pressure apparatus which could be arranged to deliver any pressure desired (fig. 3). The dogs were kept under pentobarbital sodium and morphine anesthesia during the experiments, which were carried on for six hours in nine animals and for eighteen hours continuously in the other nine. Pressures of 3, 8, 15 and 30 cm. of water and of 15 and 30 cm. of air were maintained. In one third of the dogs, the lumens

15. Perusse, G. L.: Selection of Proctoclysis Fluids, Surg., Gynec. & Obst. 54:770, 1932.

were washed clean; in one third the fecal contents were left in the lumen, and in the other third the lumens were washed, and virulent staphylococci were introduced before the cannula was tied in place. Every specimen exhibited acute pathologic changes in the extreme, amounting to gangrene in ten of the eighteen dogs. It was found that a sustained intraluminal pressure as low as 3 cm. of water over a six

TABLE 12.—*Results of Pressure Experiments of Six Hours' Duration*

Dog No.	Pressure, Cm.	Medium	State of Preparation	Edema	Hemorrhage	Gangrene	Diagnosis
119	3	Water	Washed	Grade 1	Grade 1	None	Acute appendicitis
130	8	Water	Washed	Grade 1	Grade 1	None	Acute appendicitis
121	15	Water	Washed	None	Grade 4	Grade 1	Gangrenous appendicitis
123	8	Water	Full	Grade 1	None	None	Acute appendicitis
125	15	Water	Full	None	Grade 4	Grade 1	Gangrenous appendicitis
126	8	Water	Hemolytic staphylococci introduced	Grade 1	Grade 1	None	Acute appendicitis
128	15	Water	Hemolytic staphylococci introduced	None	Grade 3	Grade 1 (?)	Acute appendicitis
97	15	Air	Washed	Grade 1	Grade 2	None	Acute appendicitis
103	30	Air	Full	Grade 1	Grade 3	Grade 1 (?)	Acute appendicitis

TABLE 13.—*Results of Pressure Experiments of Eighteen Hours' Duration*

Dog No.	Pressure, Cm.	Medium	State of Preparation	Edema	Hemorrhage	Gangrene	Diagnosis
118	8	Water	Washed	Grade 1	Grade 1	None	Acute appendicitis
120	15	Water	Washed	None	Grade 2	None	Acute appendicitis
122	8	Water	Full	None	Grade 4	Grade 1	Gangrenous appendicitis
124	15	Water	Full	Grade 1	Grade 3	Grade 1 (?)	Acute appendicitis
127	8	Water	Hemolytic staphylococci introduced	None	Grade 4	Grade 1	Gangrenous appendicitis
129	15	Water	Hemolytic staphylococci introduced	Grade 1	Grade 3	Grade 1 (?)	Acute appendicitis
109	30	Water	Full	None	Grade 3	Grade 1 (?)	Acute appendicitis
101	30	Air	Washed	Grade 1	Grade 2	None	Acute appendicitis
114	30	Air	Full	None	Grade 3	Grade 1 (?)	Acute appendicitis

hour period produced acute inflammatory changes. In this series there appears to be no direct correlation between the content of the lumen and the severity of the reaction, the pressure apparently being the more important factor. In the nine experiments of six hours' duration, four cecal appendages showed gangrene, as compared with six in the nine experiments of eighteen hours' duration (fig. 4 and tables 12 and 13).

ISOLATION OF THE CECAL APPENDAGE AS A CLOSED LOOP.—*Washed Lumens*.—In two dogs the cecal appendage was washed, severed from the cecum and inverted by two layers of suture. The appendage was thus converted into a short, clean closed loop. One of these was removed in forty-eight hours and the other after six weeks. The specimen removed after six weeks was much contracted, and its lumen contained a small amount of white mucoïd material. Microscopic sections

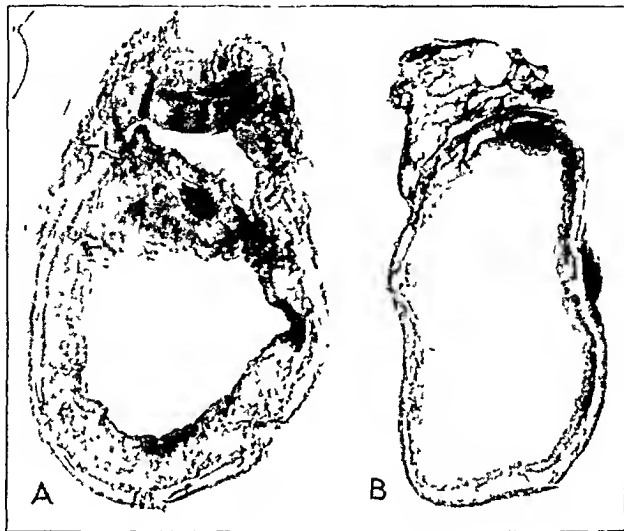


Fig. 4.—*A*, a photomicrograph showing the effect of 15 cm. of water pressure maintained for eighteen hours. *B*, a photomicrograph showing the effect of 30 cm. of water pressure maintained for eighteen hours.

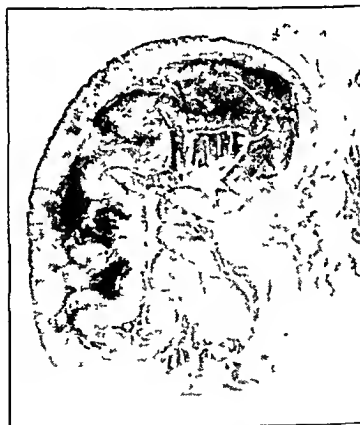


Fig. 5.—Photomicrograph of a dog's cecal appendage after it had been converted into a washed closed loop for six weeks. There are no inflammatory changes; the walls are contracted and the lumen contains a mucoïd material

failed to show evidence of inflammation in the wall. A clean closed loop of descending colon about 4 inches (10 cm.) in length was made in another dog and inspected in six weeks. Here a large cyst containing mucus had developed. Four clean closed appendical loops established in the appendixes of rabbits were normal histologically after one month (fig. 5).

Lumens Full of Fecal Matter.—In four dogs closed loops of the cecal appendage were formed with the lumens full of fecal matter. In each case the loop ruptured within forty-eight hours, and the dog died of peritonitis. Microscopic sections showed gangrenous changes. A full loop of the descending colon ruptured in thirty-six hours. Two full appendical closed loops were made in rabbits. One animal died of perforation and peritonitis in thirty-six hours. The other was operated on after four weeks. Perforation of the cecal appendage with pseudocyst formation had occurred.

THE RÔLE OF INFECTION, INVOLVING THE USE OF SPECIFIC ORGANISMS

Complete Obstruction of the Lumen for Twenty-Four Hours.—In this group five dogs were used. If fecal content could be palpated through the wall of the cecum it was carefully massaged back into the colon previous to placement of the ligature. (Obstruction by ligature of such an empty though unwashed cecal appendage, it was found, was not followed by inflammatory change.) The cecal appendage was obstructed with a ligature at its base, and 5 cc. of a broth culture of one of the following virulent organisms was injected into the lumen through a fine hypodermic needle, the site of injection being the apex of the cecal appendage: (1) *Pneumococcus* type 3, (2) *Staphylococcus aureus*-haemolyticus, (3) *Streptococcus* haemolyticus, (4) *B. Welchii* and (5) *B. pyocyaneus*. After twenty-four hours the cecal appendage of each dog was excised. All exhibited definite evidence of acute inflammation except the one into which *B. Welchii* was injected. There appeared to be a definite relationship between the degree of distention by fluid and the severity of the changes.

Stenosis of the Lumen for Twenty-Four Hours.—Again five dogs were used, and the same organisms were injected into the lumens, which were simply stenosed by means previously described in this paper. Those into which staphylococci and streptococci had been introduced showed mild acute pathologic changes, and the others were normal.

Stenosis with a Foreign Body in the Lumen for Twenty-Four Hours.—In five dogs stenosis of the cecal lumens was produced with a marble in the lumen, and the same organisms were introduced. Those into which pneumococci, streptococci and *B. pyocyaneus* were injected showed acute changes of slightly more severe degree than those described in the previous experiment.

Injection of the Same Organisms into the Wall of the Cecal Appendage.—Five minims of a broth culture of these same organisms was injected into the wall of unobstructed cecal appendages of five dogs. Forty-eight hours later the specimens were excised. Reactions similar to those attending the injection of these organisms into other tissues were observed. The injection of staphylococci was followed by the formation of a circumscribed abscess. Pneumococci produced a less localized abscess. Streptococci gave a phlegmonous reaction, *B. Welchii* a hemorrhagic area and *B. pyocyaneus* a necrotic area surrounded by a zone of green pigmentation.

Trauma to Cecal Appendage Followed by the Intravenous Injection of Virulent Organisms.—In five dogs the cecal appendages were rather severely traumatized by rubbing them between the thumb and the forefinger, and 5 cc. of the broth culture of the aforementioned organisms was injected into a vein in the leg. The cecal appendages were removed in forty-eight hours, and the walls and contents were cultured. In each case it was felt that probably the original organism was recovered, except in the case of the dog given an injection of *B. pyocyaneus*. The

experiment was repeated twice, with *B. pyocyaneus*, but in no instance could the organism be recovered. This rather suggests that the other organisms were probably resident in the cecal appendage before the intravenous injection.

It is to be noted that whereas the injection of an exudate (mixed organisms—virulent peritoneal exudate) caused acute inflammation in 100 per cent of instances in the presence of obstruction, the injection of specific organisms was effective in only 80 per cent. In the experiments in which stenosis was produced there were acute changes in 100 per cent of the appendages in the group in which the peritoneal exudate was used, in contrast to the acute changes in 40 per cent of the appendages in the group in which the specific organisms were used. Again, in the experiments

TABLE 14.—*Summary of Results of Experiments with Specific Organisms*

Time, Hr.	Procedure	Pneumo- coccus Diagnosis	Staphylo- coccus Diagnosis	Strepto- coccus Diagnosis	Cl. Welchii Diagnosis	B. Pyo- cyaneus Diagnosis
24	Complete ob- struction	Mild acute appendicitis	Gangrenous appendicitis	Mild acute appendicitis	Normal	Acute appendicitis
24	Stenosis of lumen	Normal	Mild acute appendicitis	Mild acute appendicitis	Normal	Normal
24	Stenosis and in- troduction of for- eign body	Mild acute appendicitis	Normal	Acute appendicitis	Normal	Mild acute appendicitis
48	Injection into wall	Mild acute appendicitis	Acute appendicitis	Acute appendicitis	Mild acute appendi- citis	Gangrenous appendicitis
48	Trauma to cecal appendage and intravenous in- troduction of organisms	Recovery of organism in blood and tissues	Recovery of organism in tissues	Recovery of organism in blood and tissues	Recovery of organ- ism in blood and tissues	Organism not recov- ered in blood or tissues

TABLE 15.—*Comparison of Results with Peritoneal Exudate and Specific Organisms*

Procedure	Peritoneal Exudate		Specific Organism	
	No. of Dogs	Positive Acute Changes, Percent- age	No. of Dogs	Positive Acute Changes, Percent- age
Complete obstruction.....	2	100	5	80
Stenosis of lumen.....	4	100	5	40
Stenosis and introduction of foreign body.....	9	66	5	60

in which stenosis was produced with a foreign body in the cecal appendage, there were acute changes in 66 per cent of the appendages in the group in which the peritoneal exudate was used, as compared to the same changes in 60 per cent of the appendages in the group in which the specific organisms were used. Thus, in this small series, in no case were the specific cultures as effective in producing appendicitis as was the culture of the mixed peritoneal exudate (tables 14 and 15).

INTERFERENCE WITH THE CIRCULATION OF THE CECAL
APPENDAGE

Arterial Circulation.—In one animal the main artery of the cecal appendage was ligated, and the appendage was removed in forty-eight hours. The specimen was firmly contracted and very white. Sections showed a normal appendage. In

another animal 1 cc. of a broth culture of *Staph. aureus-haemolyticus* was injected into the appendical artery, and the vein was then ligated. Within twenty-four hours the cecal appendage was acutely inflamed.

Venous Circulation.—In one dog all the veins to the cecal appendage were ligated, and the specimen was removed in forty-eight hours. There was rather marked vascular congestion, but no acute inflammatory changes in the wall.

Combined Circulation.—In two dogs the entire mesentery to the cecal appendage was cut and ligated. The specimens were removed in twenty-four and forty-eight hours. Both showed gangrene of the distal third only. These experiments seem to indicate that in the dog a considerable vascular embarrassment of the cecal appendage is fairly well tolerated, if the continuity of the lumen is not disturbed. A rich collateral circulation from the cecum through the base of the appendage explains the lack of uniform positive changes throughout the organ (table 16).

TABLE 16.—*Results of Circulatory Experiments*

Dog No.	Time, Hr.	Procedure	Gross Description	Diagnosis
99	48	Ligation of arteries of cecal appendage	Contracted and white	Normal
102	24	Injection of hemolytic staphylococci into artery	Edema and hemorrhage	Acute appendicitis
106	48	Ligation of veins of cecal appendage	Congestion in deep layers	Normal
110	24	Severance of entire mesentery	Gangrene of distal third	Gangrenous appendicitis
112	48	Severance of entire mesentery	Gangrene of distal third	Gangrenous appendicitis

TABLE 17.—*Result of Trauma to the Wall of the Cecal Appendage*

Dog No.	Time, Hr.	Gross Description	Bacteriologic Picture	Diagnosis
47	48	Few adhesions; cecal appendage empty and relaxed; blood vessels dilated; petechiae in serosa	Gram-positive diplococci; gram-negative diplococci and rods	Acute appendicitis
48	6	Bloody peritoneal fluid; cecal appendage hemorrhagic; one spot of gangrene	Acute appendicitis

MISCELLANEOUS EXPERIMENTS

Trauma to the Wall of the Cecal Appendage.—In two dogs the cecum was severely traumatized manually between the thumb and the fingers. The specimens were excised in six and forty-eight hours, respectively. Edema, hemorrhage and dense leukocytic infiltration were in evidence. The microscopic picture in these instances could not be distinguished from the acute inflammatory changes induced by the other types of experiment (table 17).

Transplantation of a Vascularized Cecal Appendage onto the Duodenum and the Descending Colon.—In two dogs the cecum was severed from the colon and anastomosed end to side to the duodenum. One was removed in ninety-six hours and the other in seven days. The sections were normal.

Two similar transplants were made onto the descending colon, the terminal few inches of the ileum with the cecum attached (after closing the cecum at

the site of section from the ascending colon) being sutured end to side to the descending colon. In such an experiment the cecal appendage was really a blind diverticular pouch of the descending colon. These pouches were excised after many weeks and were found to be distended by a mucoid material. The sections showed no evidence of inflammation (table 18).

Severance of the Cecal Appendage from the Colon.—This procedure was done in two dogs, and the lumen of the cecal appendage was left open after closing the

TABLE 18.—*Result of Transplantation of Cecal Appendage onto the Duodenum*

Dog No.	Time, Hr.	Gross Description	Bacteriologic Picture	Diagnosis
35	96	Lumen of the cecal appendage patent and continuous with that of duodenum; contents frothy and similar to that in duodenum	Very sparse organisms; gram-positive diplococci and gram-negative rods; same in duodenum and cecal appendage	Serositis
36	168	Firmly healed and anastomosis in good condition	Very rare gram-positive diplococci	Normal

TABLE 19.—*Result of Severing the Cecal Appendage from the Colon*

Dog No.	Time, Hr.	Gross Description	Bacteriologic Picture	Diagnosis
37	96	Few adhesions; no fluid or pus; cecal appendage edematous and serosa covered by exudate; lumen open and contained clear mucus	Very sparse organisms; gram-positive diplococci; gram-negative rods	Peritonitis
38	144	Many adhesions; cecal appendage sealed by omentum and covered by yellow exudate; mucus in lumen	Very sparse organisms; gram-positive diplococci	Peritonitis

TABLE 20.—*Result of the Injection of Peritoneal Exudate into the Wall of the Cecal Appendage*

Dog No.	Time, Hr.	Gross Description	Bacteriologic Picture	Diagnosis
49	36	Omentum adherent over edematous cecal appendage; hemorrhagic throughout and gangrenous at injection sites; abscesses not ruptured	Gram-positive diplococci and rods; gram-negative diplococci, rods and streptococci	Abscesses in wall
50	36	Distal abscess ruptured externally and walled off by omentum; proximal abscess ruptured internally; crater filled with yellow necrotic tissue; no perforations	Gram-positive diplococci and rods; gram-negative diplococci, rods and streptococci	Abscesses in wall

colon. These animals were again operated on in ninety-six hours and six days, respectively. There was minimal localized peritonitis. The cecal appendages contained a small amount of clear mucoid secretion containing very sparse organisms (table 19).

Injection of Exudate Into the Wall of the Cecal Appendage.—In two dogs a small amount of virulent peritoneal exudate was injected into the wall of the cecal appendage. The specimens excised after thirty-six hours showed abscesses with central areas of necrosis (table 20).

Injection of Phenol into the Lumen of the Cecal Appendage.—In two dogs 1 cc. of concentrated phenol was injected into the lumen of the cecal appendage. The appendages were excised in forty-eight hours and five days, respectively, and found to exhibit marked hemorrhage and necrosis of the inner layers with diffuse infiltration (table 21).

Measurement of Pressure Developed in Obstructed Cecal Appendages.—In ten dogs with cecal appendages obstructed for twenty-four hours, an attempt was made to measure the fluid pressure spontaneously developed within the lumen. In no instance were satisfactory determinations possible because of the viscous nature of the fluid within the lumen.

Relation of Catharsis to Perforation of the Cecal Appendage.—In eight dogs the cecal appendage was obstructed for twenty-four hours, and large doses of

TABLE 21.—*Result of the Injection of Phenol into the Lumen of the Cecal Appendage*

Dog No.	Time, Hr.	Gross Description	Bacteriologic Picture	Diagnosis
54	48	Cecal appendage edematous and serosa shows petechiae; mucosa sloughing and contents bloody	Gram-positive diplococci and rods; gram-negative diplococci and rods	Acute appendicitis
55	120	Grossly normal; mucosa sloughing and contents bloody	Gram-positive diplococci and bacilli; gram-positive spore-forming bacilli, diplococci and large bacilli	Acute appendicitis

TABLE 22.—*Effect of Release of Obstruction on Gangrenous Cecal Appendage*

Dog No.	Gross Description of Specimen		Diagnosis
	After 24 Hours of Obstruction	After 7 Days of Obstruction	
89	Gangrenous cecal appendage	Adhesions, edema and hemorrhage	Acute mild appendicitis
91	Grossly normal cecal appendage	Edema and congestion	Acute appendicitis
93	Gangrenous cecal appendage	Adhesions, edema and hemorrhage	Acute appendicitis
111	Edema and hemorrhage	Edema	Acute appendicitis
113	Edema, congestion and distention	Edema and hemorrhage	Acute appendicitis

physostigmine were given to four and croton oil to four. In every case severe diarrhea developed, but in no instance was there a perforation within twenty-four hours. Similarly, no manifest ill effects were observed from purgation with saline solution of the two dogs with the cecal appendage anastomosed to the descending colon.

Healing of Gangrenous Cecal Appendages.—In five dogs the cecal appendage was obstructed for twenty-four hours, after which the obstruction was released. Laparotomy was again performed six days later. The appendages showed rather dense omental adhesions over their surfaces and were grossly edematous. Some showed old hemorrhages, and all exhibited evidence of subsiding acute inflammatory changes. In two animals gangrene was produced by twenty-four hours of obstruction; the occluding ligature was then released, and the appendages were removed after six weeks. These were normal except for slight fibrosis of the submucosa. No strictures developed (table 22).

Bacteria in the Tissues.—In the cecal appendages excised following the maintenance of increased intraluminal pressure a variety of bacteria were found in all layers of the gangrenous specimens. The permeation of bacteria through the layers of the wall of the bowel was less evident in the nongangrenous specimens. Organisms were found in the tissues in all of the pressure experiments in which gangrene occurred. Bacteria were observed in all layers. In the nongangrenous specimens, organisms were found usually in the mucosa and the immediately subjacent layer. Sections from fifty-four representative specimens obtained in the other experiments reported on here were also studied. Bacteria were found in the tissues of the wall of the cecal appendage in only fourteen of the nongangrenous specimens. These were observed largely in the submucous and muscular layers.

COMMENT

The results of these experiments point toward two important agencies in the occurrence of inflammation in the cecal appendage, viz.: (1) obstruction and (2) infection. The pathologic picture, as it is known in appendicitis, does not occur in the cecal appendage of the dog following obstruction if the lumen is previously washed out. At the same time, infection without obstruction will not bring about the disease process. In the cecal appendage of the dog, to be sure, the factor of obstruction has to be artificially brought out, for the appendage connects with the cecum by a wide-mouthed communication. The element of infection, as in the human appendix, is, however, uniformly there in the invariable presence of bacteria. The presence of obstruction is necessary to initiate the changes, and the more complete the obstruction the more marked the changes. Invasion of the wall of the bowel by bacteria occurs as the circulatory changes progress.

The sequence of events as observed appear to mimic closely what obtains in closed intestinal loops. Such loops, first made by Whipple¹⁶ and his associates to study the phenomena accompanying obstruction of the bowel, have taught much relative to the behavior of the bowel under conditions of obstruction. Owing to continued profuse secretion from jejunal loops, they usually rupture, as absorption of fluid at this level in the bowel is not as prominent as secretion. Burget and his associates¹⁷ had dogs survive with closed loops of small intestine, however, for relatively long periods of time when they frequently aspirated the content accumulating within the loop. In the main, the shorter the loop, the greater is the hazard of perforation. Whereas closed loops of colon containing feces are likely to rupture, short, washed closed loops of colon appear to give no trouble. This would appear, also, to

16. Stone, H. B.; Bernheim, B. M., and Whipple, G. H.: *Intestinal Obstruction: A Study of the Toxic Factors*, Bull. Johns Hopkins Hosp. **23**:159, 1912.

17. Burget, G. E.; Martzloff, K. H.; Suckow, G. R., and Thornton, R. C. B.: *The Closed Intestinal Loop: The Relation of Intraloop (Jejunum) Pressure to the Clinical Condition of the Animal*, Arch. Surg. **21**:829 (Nov.) 1930.

be the significant mechanism in the experimental production of inflammation of the cecal appendage.

The late Van Zwalenburg¹⁸ was one of the first to point out the significance of the obstructive factor in the experimental production of inflammation in the cecal appendage of the dog. In 1904 he published the results of experiments in which he maintained distention of the cecal appendage of the dog over a period of four hours under a constant intraluminal pressure of 150 mm. of mercury. After the lapse of twenty-four hours, the specimen was excised; gangrenous changes were usually present. In our study we found that relatively low pressures (from 8 to 15 cm. of water) maintained from six to eighteen hours will bring about gangrenous changes. In ileal closed loops 18 inches (45.7 cm.) in length subjected to a constant sustained intraluminal pressure of 20 cm. of water from twenty-eight to thirty-two hours, Sperling and Wangenstein¹⁹ observed *necrosis of the wall with accompanying loss of viability and evidence of abnormal permeability of the tissue*. When a pressure of 40 cm. of water was employed, similar changes were obtained in seventeen hours.

Boit and Heyde²⁰ and Heile²¹ and more recently Eichoff and Pfannenstiel²² also concluded that obstruction is an important item in the experimental production of a picture akin to that observed in appendicitis. The literature is large, and no attempt will be here made to review it systematically.

CLINICAL OBSERVATIONS

This study has dealt essentially with the experimental features of the problem. During this same time, however, opportunity has been afforded for clinical observations which permit of conclusions which tend to corroborate the thesis relating to the significance of the obstructive factor set forth in this experimental investigation. The pathologic

18. Van Zwalenburg, C.: Obstruction and Consequent Distension the Cause of Appendicitis as Proved by Cases and by Experimental Appendicitis in Dogs, J. A. M. A. **42**:820 (March 26) 1904.

19. Sperling, Louis, and Wangenstein, O. H.: Unpublished data

20. Boit, H.: Experimentelle Entzündung des Blinddarmhanges beim Hunde, Verhandl. d. deutsch. Gesellsch. f. Chir. **42**:234, 1912; Berl. klin. Wchnschr. **49**: 812, 1912. Boit, H., and Heyde, M.: Experimentelle Untersuchungen zur Aetiologie den Wurmfortsatzentzündung, Beitr. z. klin. Chir. **79**:271, 1912.

21. Heile, B.: Ueber die Folgezustände nach mechanischem Abschluss des Blinddarmhanges bei Mensch und Thier, Verhandl. d. deutsch. Gesellsch. f. Chir. **42**:228, 1912; Ueber die Entstehung der Entzündungen am Blinddarmhang auf bakteriologischer und experimenteller Grundlage, Mitt. a. d. Grenzgeb. d. Med. u. Chir. **26**:345, 1913; Experimentelle Appendizitis, München. med. Wchnschr. **6**:209, 1925.

22. Eichoff, E., and Pfannenstiel, W.: Experimentelle Untersuchungen zur Aetiologie der Appendizitis, Beitr. z. klin. Chir. **151**:171, 1930

aspects of the clinical problem will be elaborated on by one of us (W. F. B.) at a later date. The clinical observations here related were made on patients in the surgical wards of the Minneapolis General Hospital (W. F. B.).

During the current year, the operative specimens from ninety-one patients with conditions diagnosed pathologically as acute appendicitis were available for examination. With the cooperation of the operating surgeons, it was possible to get appendixes on which no clamps had been placed during the procedure of operative removal. The gross appearance of the appendix was carefully noted, and great care was taken not to traumatize it by palpation. The specimen was then placed in a diluted solution of formaldehyde (1:10) and allowed to stand for twenty-four hours before it was cut. At this time the appendix was slit longitudinally with a sharp Bard-Parker knife much in the manner in which one bivalves a plaster cast, leaving anterior and

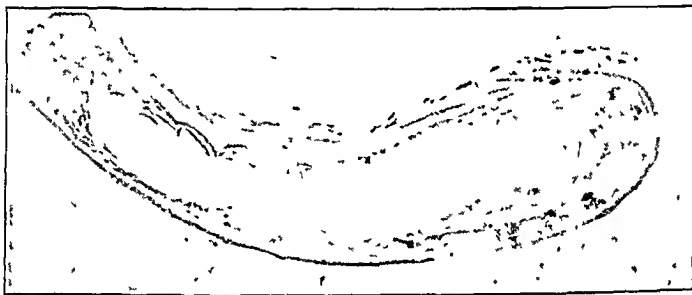


Fig. 6.—Photomicrograph of a section of an obstructed gangrenous appendix showing the distal dilatation, thinning of the wall, thrombosis of vessels and erosion of the mucosa. Proximal to the area occupied by the fecalith, the wall is shown to be practically normal; dilatation of the lumen is absent.

posterior shells. The presence or absence of appendical concretions, narrowing or dilatation of the lumen, the presence of strictures and the state of the appendical wall at various places were all carefully noted. Histologic examination of the tissues were made in representative areas in the manner outlined in this experimental study.

The gross appearance of the ninety-one appendixes led to the following pathologic classification as to the type of appendicitis: acute suppurative appendicitis, forty-three cases; nonperforative gangrenous appendicitis, nineteen, and perforative gangrenous appendicitis, twenty-nine. Clinically, the cases in which collections of free exudate were found outside the appendix at the time of operation all belonged to the group of cases of perforative appendicitis. The only fatalities, as one might well anticipate, occurred in this group. In three of the fatal cases the patient died of suppurative complications consequent on peritoneal infection (figs. 6 and 7).

Of the forty-three cases of acute suppurative appendicitis, an appendical concretion had caused a definite obstruction in eighteen, or 44 per cent. In the thirteen additional cases obstruction appeared to have developed through the agency of a stricture, a sharp kink or an abnormal band. When these extrinsic obstructive phenomena are included with the intrinsic obstructions, the total for the group is 72 per cent. Of the forty-eight cases of gangrenous appendicitis, an appendicolith had brought about an obstructive mechanism in thirty-eight, or 80 per cent. Of the ten remaining cases, a stricture or definite extrinsic



Fig. 7.—Photomicrograph of a section of the appendix in figure 6 showing the necrotic changes just distal to the point of obstruction.

obstruction was present in every instance, establishing an obstructive causative mechanism in 100 per cent of the cases.

The fecaliths were large brownish bodies; in many instances there were more than one. Occasionally, these concretions were grayish white and unusually hard. On cut section, they were always laminated, indicating that they had formed rather gradually and had probably attained an age considerably beyond that of fecal masses in the bowel. A central nucleus of a bit of undigested cellulose from the intestinal canal, or less commonly a foreign body such as a tooth brush bristle, was

the rule. Several of these appendical concretions were subjected to chemical analysis for bilirubin, urobilin, urobilinogen and copronegrin. These tests, which were performed for us by Dr. Cecil J. Watson, were negative for bile pigment. These observations tend strongly to support the impression that these concretions arose essentially in the appendical lumen, even though the nucleus came from the intestinal canal. The formation of such enteroliths in the intestinal canal under conditions of stasis is well known. Such an occurrence would suggest that the appendix may frequently behave somewhat as a closed loop as far as the remainder of the intestinal canal is concerned, at times permitting material to enter but precluding free extrusion of intestinal content from it ²³ (figs. 8 and 9).



Fig. 8.—Longitudinal section of an acutely inflamed appendix showing a large laminated fecalith obstructing the lumen. Distal dilatation of the lumen with mucosal ulceration is seen. These changes are not present proximal to the obstruction.

One of us (O. H. W.), with the cooperation of Dr. Wallace Ritchie, resident surgeon, and other house officers at the University Hospital, has recently subjected this premise to experimental inquiry. When the uninflamed appendix was removed in the interval, opportunity was afforded to determine whether the appendix might behave as a closed loop. A needle attached to a column of water was inserted into the appendical lumen at the distal end. Invariably the pressure of a column of water 40 cm. in height could be supported without a drop of water running into the cecum. In many instances a pressure of from 60 to 80 cm. of water would be sustained. In a few instances in which there

23. Dr. G. E. Burget, professor of physiology at the University of Oregon Medical School, who has studied "closed loops" over a prolonged period, informs us that lamination was never observed in the material which formed in such loops.

had been previous inflammation, a column of water of more than 100 cm. in height failed to cause the water to enter the cecum. In preparations of the cecum and appendix, as obtained at autopsy, it was uniformly observed that lesser pressures were withstood. The latter finding suggests that the obstacle to inflow of water from the appendix into the cecum may be occasioned by a sphincter-like mechanism. In 1847 Gerlach²⁴ suggested the presence of such a valve, but its action as a sphincter has been denied by anatomists. These observations lend tenable support for the existence of such a mechanism. How in turn



Fig. 9.—Longitudinal section of a completely gangrenous appendix which had spontaneously amputated itself at the cecum. The fecalith at the tip is maintained in its position by a connective tissue stricture. The second fecalith was found free in the abscess surrounding the appendix.

a sphincter-like mechanism may be reflexly influenced through its extrinsic nerve supply is a matter which permits of some speculation. The findings relating to this study will be described elsewhere at greater length.

COMMENT

In the early literature on appendicitis, the significance of the mechanical element in the occurrence of perforation of the appendix enjoyed more credence than it does today. In an admirable little monograph,

24. Gerlach, L.: Beobachtung einer tödliche Peritonitis als Folge einer Perforation des Wurmfortsatzes, *Ztschr. f. path. Med.* 6:12, 1847.

too little known, written by Adolph Volz²⁵ in 1846, the importance of the appendical concretion in the complication of perforation received full recognition. Volz expressed the belief that perforation occurred through the agency of pressure erosion over the concretion, and even today one occasionally hears of this causal relationship between the appendicolith and the perforation. Those familiar with the behavior of closed loops know that whereas perforation may occur near the site of occlusion, in the main, rupture is more likely to occur at the weakest point between the two ends of the short loop.²⁶ Matterstock²⁷ in 1880 and Fitz¹ in 1886 again gave important consideration to the obstructive element in the occurrence of perforation of the appendix, as did Maaloe²⁸ also in 1908. More recently Wilkie²⁹ designated clinical cases of appendicitis as instances of acute suppurative appendicitis and of appendicular obstruction. Cutler,³⁰ Westphal³¹ and Williams and Boggon³² have again recently emphasized the importance of the mechanical factors in the genesis of appendicitis.

Meleney and his associates,³³ in a splendid paper on the subject of suppurative appendicitis, pointed out that deaths as well as the complications of appendicitis occurred almost solely in the cases in which the appendix perforated. In a recent communication, Meleney³⁴ wrote: "You are quite right in believing that I feel that fecal concretions in the appendix are frequently responsible for the initiation of appendiceal inflammation."

25. Volz, A.: Die durch Kothsteine bedingte Durchbohrung des Wurmfortsatzes, die häufig verkannte Ursache einer gefährlichen Peritonitis und deren Behandlung mit Opium, Carlsruhe, C. F. Müller, 1846.

26. Van Beuren, F. T.: Mechanism of Intestinal Perforation Due to Distension, *Ann. Surg.* **83**:69, 1926.

27. Matterstock, G. K.: Perityphlitis, in Gerhardt, C.: *Handbuch der Kinderkrankheiten*, Tübingen, H. Laupp, 1880, vol. 4, pp. 2 and 893.

28. Maaloe, C. U.: *Histopatologiske studier over processus vermiformis*, Kommission hos Jacob Lund, Kjøbenhavn, 1908.

29. Wilkie, D. P. D.: Acute Appendicitis and Acute Appendicular Obstruction, *Brit. M. J.* **2**:959, 1914.

30. Cutler, O. I.: Mild Acute Appendicitis: Appendical Obstruction, *Arch. Surg.* **31**:729 (Nov.) 1935.

31. Westphal, K.: Appendizitis und Kotstein als Folge gestörter Appendixfunktion, *Deutsche med. Wchnschr.* **60**:499 and 600, 1934.

32. Williams, B. W., and Boggon, R. H.: Mechanics of Appendicitis, *Lancet* **1**:9, 1934.

33. Meleney, F. W.; Harvey, H. D., and Jern, H. Z.: Peritonitis: I. The Correlation of the Bacteriology of the Peritoneal Exudate and the Clinical Course of the Disease in One Hundred and Six Cases of Peritonitis, *Arch. Surg.* **22**:1 (Jan.) 1931.

34. Meleney, F. W.: Personal communication to the authors.

The increased intraluminal tension in the gallbladder occasioned by impaction of a calculus in the cystic duct and the occurrence of gangrene in the cecal wall consequent on obstruction of the pelvic colon and the closed loop so formed, owing to the competence of the proximal ileocecal sphincter as well as the gangrene occasionally observed in the urinary bladder as the result of infection, attest the importance of the mechanical element for the occurrence of perforation in the obstructed appendix.

Another place in the intestinal canal where one commonly sees perforation, as a consequence of obstruction and infection, is in the crypt of the anorectal region, inflammation of which not infrequently eventuates in ischiorectal abscess and an external rectal fistula. The significance of the mechanical element for this sequence of events is at once apparent. Prominent lymphatic follicles intervene between the semilunar pockets. Normally a free secretion of mucus serves to extrude any small particles which find their way into them. The lodgment of foreign bodies in these pockets readily sets up inflammatory changes in the lymphoid follicles, which in turn swell and further preclude extrusion of the foreign body. Perforation of the rectal wall occurs as a direct consequence. In the occurrence of this sequence of events, appendicitis probably has a close counterpart. The suggestion of Aschoff that the crypts of Lieberkühn in the empty appendix make good hiding places for small foreign bodies as well as bacteria is particularly good. Obstruction, however, would appear to be the factor of greatest moment in permitting such foreign bodies or bacteria to find their way through the coats of the appendical wall. Similarly swelling of the lymphoid tissue in the nasopharynx undoubtedly plays an important rôle in obstructing the eustachian tube and in causing perforation of the ear drum in otitis media.

The clinical picture itself in acute appendicitis accentuates the importance of the mechanical features. It is essentially early a colic in which a febrile disturbance, usually of low grade, indicates the onset of inflammation and suppuration consequent on the obstruction.

The more prevalent medical opinion, however, appears to be that in most instances acute appendicitis is of infectious origin.³⁵ The expressions of Aschoff on this subject have undoubtedly been important in throwing into practical discard the older ideas relating to the significance of the obstructive element. The suggestion of a specific infection is most intriguing. And to be certain, one sees clinical examples which would lend credence for the possibility of such an

35. Fonio, A.: *Zur Frage der Kontagionsmöglichkeit der Appendicitis*, Schweiz. med. Wchnschr. **58**:597, 1928. Walther, K.: *Zur Infektiosität der Appendicitis: Untersuchungen über epidemieartiges Auftreten im Reichsheer*, Arch. f. klin. Chir. **166**:72, 1931. Adrian.⁵ Rosenow.⁸ Aschoff.^{9c}

occurrence in the appendix, viz., the epidemics of infection of the upper respiratory tract in which the incidence of laryngitis or tracheitis is uniformly high or the instances in which the occurrence of intestinal cramps and diarrhea are frequent, and others in which vomiting is a frequent disturbance. However interesting may be the finding by Aschoff of a relatively pure culture of an organism in the distal third of the normal appendix, uncontaminated by the more sociable organisms in the more proximal reaches of the appendix, the finding of this bacterium as the sole or the predominant organism present in the suppurative process of appendicitis does not establish appendicitis as a specific bacterial disease. Such organisms do not produce inflammation in the cecal appendage of the dog unless it is obstructed, and most investigators have found that a number of organisms may be present in the acutely inflamed appendix, as did also Aschoff at times. What the factors are which incite the organisms to activity have not been clarified. It is our belief that the usual provocation is obstruction, and our observation has been that a number of bacteria, corresponding to the flora of the bowel, may be found in the suppurative process. The bacteriologic features of the problem will be elaborated on later by one of us (W. F. B.). What the explanation of so-called epidemics of appendicitis is is not apparent. In the main, statistical studies indicate that appendicitis divides itself fairly evenly throughout the year.

THE PROBABLE SEQUENCE OF EVENTS IN APPENDICITIS

The facts which stand out prominently concerning the human vermiform appendix are that it is a very narrow, hollow tube, closed at its far end with an unusual amount of lymphoid tissue in its wall. It would also appear that the appendix is a potential closed loop, in that something akin to a sphincter-like mechanism at its juncture with the cecum interferes with evacuation of material which has found its way into the appendix. The occurrence of obstructive appendical concretions in the lumen in a large percentage of all cases of acute suppurative appendicitis suggests the presence of such a mechanism. These concretions are usually laminated, indicating that they have been some time in forming. They do not react positively to any of the usual tests for bile pigments. Even though the central nucleus comes from the intestinal canal, the larger portion of these concretions are formed in situ. That acute suppuration of the appendix may occur on the basis of obstruction in the absence of such concretions appears likely in that the appendix apparently behaves like a potential closed loop. With evacuation of the content of the appendix interfered with, a struggle for hydraulic equilibrium ensues in the lumen. Blood comes into the appendix under the motive force of systolic blood pressure. When the sphincter-like

mechanism at the base of the appendix resists evacuation of its content, the lumen distends. The increase in intraluminal pressure interferes with venous return; with maintenance of sustained intraluminal pressure for a few hours, the tiny veins rupture and hemorrhage occurs. Owing to the poor oxygenation of the tissue, it is a matter of no great difficulty for the ever present bacteria to invade the submucosal lymphoid tissue. The swelling is thereby increased, and the inflammatory process is in full swing.

If bacteria were not present in the lumen of the appendix its obstruction would be no more hazardous than the strangulation of a small ovarian cyst or torsion of a testis.

SIGNIFICANCE OF THE OBSERVATIONS HERE REPORTED

The surgeon has become rather apologetic over operating for the removal of an acutely inflamed appendix when operation failed to disclose an obviously menacing organ. He has in a sense become the sensitized victim of the pathologist, who is likely, when he fails to find evidence of acute inflammation in the appendix, to decry the operation as having been unnecessary. More and more, however, the significance of altered function must become a consideration important to the pathologist as well as to the surgeon.

The serious threat always latent in the bad anatomic arrangement of the appendix, which man gives no immediate promise of outgrowing, fully justifies its prophylactic removal during the course of other abdominal operations, where this procedure may be done without additional risk. In the presence of pain in the right side of the abdomen, when other causes have been adequately excluded, the removal of the appendix in the absence of previous acute attacks would appear to be fully justified, pathologic opinion to the contrary notwithstanding. Now it is significant that C. W. Mayo,³⁶ before the Western Surgical Association two years ago, reported satisfactory relief from symptoms after appendectomy in more than 70 per cent of patients with indefinite pain on the right side of the abdomen, when a careful preoperative examination excluded other palpable causes. Sources for abuse in the advocacy of promiscuous appendectomy are obvious. The surgeon with an alert and knowing conscience is not likely to advise the operation, however, without just cause. When one recalls that between 18,000 and 20,000 persons die every year from acute appendicitis in this country alone, it is apparent that physicians and patients have given too little credence to the serious import of appendical colic.

36. Mayo, C. W.: Exploration of Abdomen and Appendectomy for Atypical Symptoms: Results Five Years After Operation in One Hundred Cases, *West. J. Surg.* **42**:189, 1934.

Aschoff pointed out that autopsy discloses that from 75 to 80 per cent of appendixes in persons in the sixth or seventh decade of life show evidence of previous inflammation.^{9b} Obliteration may be observed even in the first decade of life. It is not a physiologic process; it does not happen in the fallopian or eustachian tube or in the urethra or ureter in the absence of an ulcerative process. A ureter maintains its lumen indefinitely after nephrectomy. That appendicitis is a common ailment is therefore at once apparent.

The appendix of the infant frequently maintains the fetal funnel-like attachment to the cecum for the first few years of life. The minute anatomy of the appendix must be carefully scrutinized. In its better understanding, undoubtedly, are to be found facts yet unknown which relate themselves to the problem of appendicitis. Such studies are now under way in the University Hospital Clinic. It appears likely that the anatomy of the appendix is a far more responsible agent in the causation of appendicitis than is the diet.

CONCLUSIONS

From this study we feel that the following conclusions are justified:

1. Obstruction and infection are the two causative factors important in bringing about the picture of acute appendicitis. In the dog complete obstruction of the infected cecal appendage was always followed by inflammation; obstruction of the washed appendage was usually well tolerated. Infection without obstruction did not produce inflammation.

2. The essential inciting factor would appear to be a disturbance in the pressure-distention relationship of the appendix. Sustained intraluminal pressures of from 8 to 15 cm. maintained for from six to eighteen hours invariably were followed by changes in the wall of the cecal appendage.

3. There appears to be a sphincter-like mechanism at the base of the appendix which makes of it a potential closed loop, with all its attendant inherent dangers. This mechanism accounts for the formation of appendical stones or concretions. These are laminated and are formed largely in situ in the appendix, a sign of appendical stasis.

4. Appendical concretions are found as acutely obstructing agents in most instances of perforated appendixes—the group in which mortality occurs.

5. Appreciation of the significance of appendicular colic should lead to a better understanding of the nature of appendicitis. Appendicular obstruction brooks no delay and demands immediate appendectomy.

THE MANAGEMENT OF COMPOUND FRACTURES

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The management of compound fractures is by no means standardized. The methods of treatment are many and varied, although fundamentally the principles are the same. No one method is applicable to all compound fractures. Before deciding on the procedure, consideration must be given to the location and type of fracture, to the condition of the patient and of the wound and to the posttraumatic time factor.

In 1794 Weldon¹ wrote that the "principles in the management of compound fractures" were:

1. To stop hemorrhage.
2. To reduce the bones to their proper situation.
3. To bring every part of the wounded surface into close contact with its opposite surface.
4. To retain both the bones and soft parts in their proper situation until they are united.
5. To moderate the violence of the inflammation.

These principles still hold good.

THERAPY

A compound fracture is an emergency and requires immediate attention. The treatment resolves itself into the care of (1) the patient, (2) the wound and (3) the fracture.

The patient in shock should be treated accordingly, since the local treatment is of no consequence if the patient dies in shock. Active bleeding must be arrested. The patient is placed in the shock position and external heat is applied. Morphine, codeine or a mixture of the hydrochlorides of the opium alkaloids is invaluable for the relief of pain or anxiety. In a fracture of the long bones, traction on the limb or splintage allays pain and helps in the prevention of shock. The fluid balance and blood pressure are maintained by the administration of fluids subcutaneously or intravenously. For hypodermoclysis, physio-

Read before the Surgical Section of the New York Academy of Medicine, March 6, 1936.

1. Weldon, Walter: *Observations, Physiological and Chirurgical, on Compound Fractures, Containing an Answer to the Following Question: "What Are the Best Methods of Treating Compound Fractures, According to the Degree of Injury Sustained by the Limb?"* Southampton, B. Crosby, 1794, vol. 7.

logic solution of sodium chloride or a 2 per cent solution of dextrose in physiologic solution of sodium chloride is advisable, while for infusion, either physiologic solution of sodium chloride or a 10 per cent solution of dextrose may be used. Transfusion of whole blood from a suitable donor is invaluable, especially after hemorrhage.

As soon as the patient has reacted, 1,500 units of tetanus antitoxin are given subcutaneously. The antitoxin should be injected slowly, and one should be on guard for the possibility of an anaphylactic reaction. The administration of a prophylactic dose of polyvalent gas gangrene antitoxin together with the tetanus antitoxin is recommended. My associates and I have been using 2.5 cc. of the Lederle product, which contains *Bacillus perfringens*, *Bacillus Welchii* and *Bacillus oedematis-maligni* antitoxin. In our series of 100 cases there has not been a case of tetanus or of gas gangrene.

In the treatment of a compound fracture much depends on the time element. If a patient is treated within six hours after trauma, provided satisfactory débridement can be done, immediate suture of the wound without drainage is our method of choice. Subsequent to this period the wound should be left wide open or loosely sutured and drained.

As soon as the patient is seen, the wound is covered with a sterile dressing or a towel. If possible, roentgenograms are taken and studied before local treatment is attempted. It is necessary to note the condition of the circulation and to ascertain the presence of any damage to the nerves or tendons. Local treatment should be carried out under superaseptic precautions and with the patient under anesthesia. Grease and grime in and about the wound are removed with gasoline, benzene or kerosene. The wound is then protected with a pad soaked in alcohol. The surrounding skin is gently washed with soap and warm sterile water. The washing should be careful, painstaking and nontraumatic, so as to avoid the dissemination of infection and to prevent further insult to already traumatized tissue. The skin is then carefully dried and painted with tincture of iodine. The pad covering the wound is now removed. The wound is gently washed with warm sterile water and soap, and this procedure is followed by flushing with hot ether. When the wound has become fairly dry, it is flooded with tincture of iodine. Of 100 patients so treated, infection developed in only 9. I feel that this relative freedom from infections is due to the proper washing and gentle handling of the part and not to the use of so-called antiseptics. I believe that all physicians are in accord with the fact that too much should not be expected from the use of antiseptics. After the part has been properly cleansed, foreign bodies are removed, and all devitalized or bruised tissues are excised. Loose pieces of bone, when covered by periosteum, should be retained.

Débridement should consist of the complete removal of actually damaged tissue and not in the sacrifice of a great deal of healthy tissue, as practiced during and immediately after the World War. I am in favor of excising small wounds and then enlarging them so as to allow for free inspection of the deeper structures. Débridement as such was first mentioned by Larrey,² who was chief surgeon to Napoleon's army.

Severed nerves and tendons are immediately repaired. Otherwise, there should be little suturing of the deep structures and then only with catgut. The skin is closed with interrupted dermal sutures so placed and tied as to allow for swelling and drainage. Tight closure will cause aseptic necrosis and a resultant loss of tissue. The fracture is then treated as a simple one. Deep and bloody wounds should be drained with rubber tissue or a pipe cleaner. Pipe cleaners as drains were first brought to my attention by Moorhead.³

In cases in which the edges of the wound cannot be approximated without tension, releasing incisions should be made on one or both sides of the original wound and the original wound closed. If necessary, the subsequent incisions are allowed to remain open. This procedure covers the bone with healthy tissue.

Primosecondary suturing of the wound, as recommended by Moorhead,³ should be seriously considered. According to the technic advised by him, interrupted nonabsorbable sutures are introduced but are not tied. A sterile dressing is applied to the wound, and if at the expiration of from forty-eight to seventy-two hours there is no evidence of infection, the sutures are tied. Union by primary intention follows.

When the wound cannot be closed because of badly contused tissues or a marked loss of soft structures, one is confronted with a serious problem. If the bone remains exposed, necrosis follows. Under these circumstances I believe that the Orr treatment is the method of choice. As soon as healthy granulations appear, the wound should be covered with pinch grafts. Early skin grafting lessens the period of disability.

In a compound fracture of the skull the scalp is shaved and then prepared as described. The edges of the wound should be excised, bleeding carefully attended to and any detached fragments of bone, dirt and hair removed. Depressed bone should be elevated if focal signs of infection are present. Torn dura should be closed, if possible. I am in accord with Temple Fay,⁴ who stated: "The one clear-cut

2. Larrey, D. J.: *Mémoires de chirurgie militaire et campagnes*, Paris, J. Smith, 1812.

3. Moorhead, John J.: Personal observation.

4. Fay, Temple: *The Treatment of Acute and Chronic Cases of Cerebral Trauma, by Methods of Dehydration*, *Ann. Surg.* **101**:76 (Jan.) 1935.

indication for prompt surgery after cranial trauma is the presence of a compounded fracture of the skull, where foreign bodies, fragments of bone, hair or dirt may have entered the brain substance. Here the first principle is cleanliness and protection of the brain structures against infection. Débridement and proper repair of the wound should be done as promptly as possible, instituting appropriate drainage if necessary."

In the management of compound fractures, differences of opinion existed a century and more ago as they do today. As previously mentioned, Larrey² advised early débridement and closure. Beaumont⁵ one hundred and five years ago, in discussing the treatment of compound fractures, wrote: "It appeared to me, that by maintaining in compound fractures a continued exclusion of the atmosphere from the broken surfaces of the bone, union might proceed, *ceteris paribus*, as rapidly as in simple fractures, and with almost as little danger." He recommended a dressing of the wound and condemned the use of splints. He further stated that "by incrusting in Plaster of Paris a fractured leg" shortening is prevented. In concluding the article, he wrote: "If against the mode I have proposed of treating compound fractures, it should be urged that one cannot daily examine the limb in order to ascertain its state, I would say that any examination of the local malady must be unnecessary so long as there is little constitutional disturbance. . . ." Walker⁶ in 1845 recommended free drainage and the open treatment. Recently, Sherman⁷ expressed the belief that if the fracture cannot be reduced the wound should be enlarged and reduction obtained and maintained by the use of plates and screws, but he opposed utilizing encircling bands and wires. He advised removal of plates in about four to five weeks after bony fixation has occurred. In his opinion, extensively comminuted fractures should not be operated on, treatment by traction and suspension being preferable. Pfeiffer and Smyth⁸ are strong advocates of the Orr treatment for compound fractures.

In a fracture of the long bones, immediate traction should be made on the limb to prevent shock, to obliterate dead spaces and to avoid the collection of blood and serum therein. "Splint 'em where they lie"

5. Beaumont, W. Rawlins: *Observations and Experiments on a New Mode of Treating Fractures of the Leg and Forearm, Especially Compound Fractures*, London, Longman and others, 1831, p. 8.

6. Walker, W. J.: *An Essay on the Treatment of Compound and Complicated Fractures*, Boston, Crocker & Brewster, 1845, p. 8.

7. Sherman, W. O'Neil: *The Operative Treatment of Fractures*, in Nelson Loose-Leaf Surgery, New York, Thomas Nelson & Sons, 1927, vol. 3, pp. 405-457.

8. Pfeiffer, D. B., and Smyth, C. M., Jr.: *The Treatment of Compound Fractures with Special Reference to the Orr Method*, *Ann. Surg.* **102**:1059 (Dec.) 1935.

is good advice in all fractures of long bones. It is of the greatest importance in compound fractures, since proper early splintage will prevent the dissemination of infection within the tissues and avoid further trauma to the soft parts by the fragments.

Protruding bone should be carefully inspected before being replaced. If the ends are soiled, scrubbing with soap and warm water is allowable. When a fracture can be reduced by manual manipulation, this should be done before the wound is closed. Reduction is maintained by encasing the part in plaster of paris. When necessary, a window is cut in the cast to allow for the removal of drains and for the dressing of the wound.

In a fracture with overriding or with much comminution the procedure is traction and suspension. The introduction of a Kirschner wire is a simple operation, causing practically no destruction to either the soft structures or the bone. It is introduced through healthy bone distal to the site of the fracture. By paying careful attention to the alinement of the limb and by taking repeated roentgenograms, one can guide the position of the fragments. Dressing of the wounds is easy and can be done with little or no discomfort to the patient. When the overriding has been corrected and reduction obtained, the following procedures may be employed:

1. The part may be allowed to remain in suspension with lessened traction until union of the fragments has occurred. During traction, one must guard against distraction of the fragments.

2. The part may be immobilized in a plaster of paris cast, the traction wire being allowed to remain in situ. After seventy-two hours, roentgenograms are taken. If the fragments have not slipped, the traction wire may be removed.

In our series of 100 cases of fracture, the two sites that gave the poorest end-results were: (1) both bones of the leg and (2) the bones of the hand. It should be borne in mind that because of the anterior bowing of the tibia, the weight-bearing line of the leg runs slightly anterior to the middle of the ankle joint. When dishing occurs, the weight-bearing line moves backward, and the weight of the body is carried on the heel. The muscles of the calf are stretched over the angulated bone and pull on the os calcis so as to bring the heel up and the toes down. As a result, the function of the part is limited and painful. It is evident, therefore, that in the treatment of a fracture of the leg, the normal anterior bowing of the tibia must be retained or even slightly exaggerated.

All of our compound fractures of the bones of the hand were due to crushing violence. Most of the wounds were covered with grease and grime. The tissues were so distorted that satisfactory débridement



Fig. 1.—Roentgenogram showing a fracture of the shafts of the metacarpals of the third, fourth and fifth fingers, with marked displacement. (Published through the courtesy of Dr. John J. Moorhead.)

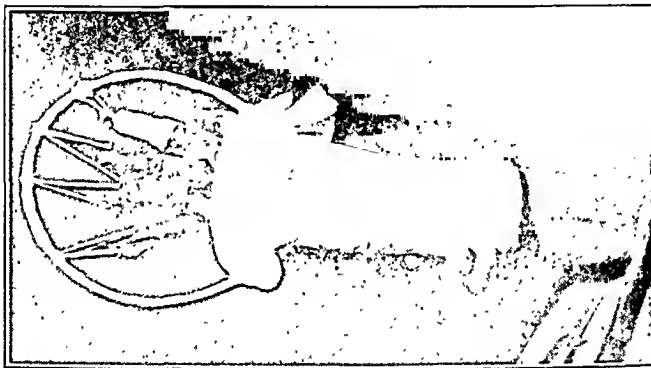


Fig. 2.—The method used for obtaining traction in a case of fracture of the shafts of the metacarpals. (Published through the courtesy of Dr. John J. Moorhead.)

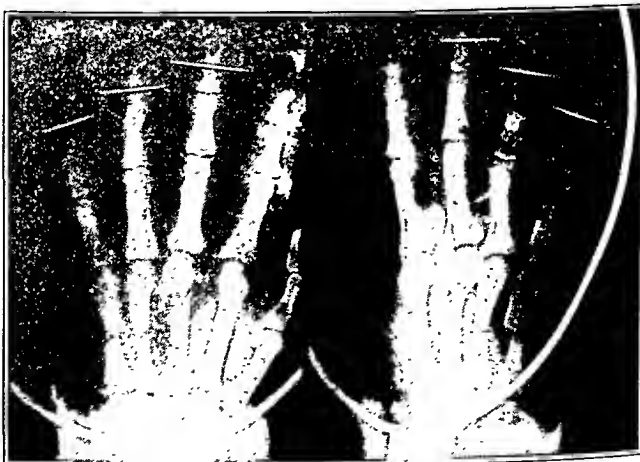


Fig. 3.—Roentgenogram showing the reduction obtained by the method described. Note the needles through the terminal portions of the phalanges of the third, fourth and fifth fingers. (Published through the courtesy of Dr. John J. Moorhead.)

was impossible. Yet, infections were surprisingly infrequent. Fractures of the metacarpals and phalanges are best treated by traction and suspension (fig. 1). A banjo splint is applied to the flexor surface of the forearm (fig. 1). Sure and steady traction can be made by passing a stout silk thread through the finger-nail or about a needle through the pulp of the fingers or terminal portion of the phalanges (fig. 2). The thread is then fastened and tied to the splint. Traction can be increased by twisting the thread in the manner of a Spanish windlass. The normal concavity on the flexor surfaces of the metacarpals and phalanges must be maintained; it can be done by stretching a piece of bandage across the splint and resting the flexor surface of the fracture on it. Obviously, dressing of the wound is simple. Figure 3 shows the reduction obtained.

ANALYSIS OF FRACTURES

Fifteen per cent of all the fractures seen at the New York Post-Graduate Hospital and the Reconstruction Hospital over a five year period were compound. From a study of 100 compound fractures, we obtained the following data:

Sex Incidence	
88 male	12 female

Age Incidence (no. of patients)	
1 yr. to 10 years	6
10 " " 20 "	6
20 " " 30 "	33
30 " " 40 "	18
40 " " 50 "	24
50 " " 60 "	7
60 " " 70 "	6

Sites of Fracture (no. of cases)	
Skull	21
Lumbar portion of spine	1
Jaw	4
Nasal bones	6
Humerus	6
Radius and ulna	6
Metacarpals and phalanges	18
Femur	6
Tibia and fibula	26
Tibia	3
Pott's fracture	3

Causes	
Automobile accidents	74 fractures
Other violences	26 fractures, of which 1 was the result of a bullet

Infections (total, 9 cases)

Moderate; subsided without involvement of bone....	4
Severe	2
Osteomyelitis, which responded to treatment.....	2
Osteomyelitis, which did not respond to treatment and eventually came to amputation.....	1

Malignant Growth

Development of a carcinoma at the site of fracture,
involving the tibia and necessitating amputation... 1 case

Amputations (Total, 3 Cases)

1. Immediate, due to the marked loss of soft structures and bone
2. Late, for chronic osteomyelitis and a hopelessly functionless extremity
3. Late, for carcinoma of the leg

Deaths (Total, 8 Cases)

Death without the patient reacting from shock.....	3
(In all 3 cases there were multiple injuries.)	
Death twenty-four hours after admission and following operation for ruptured spleen	1
Death five weeks after accident.....	1
(No autopsy was obtained; patient apparently died from a pulmonary embolus.)	
Death from fulminating infections.....	2
(In both cases the infections were due to mixed staphylococci and streptococci.)	
Death following amputation for infection of compound fracture.....	1

CONCLUSIONS

A compound fracture is an emergency and requires immediate treatment.

The treatment must be directed toward the care of first the patient and then the part.

In the prevention of infection, more is to be expected from proper washing than from the so-called antiseptics.

Immediate splintage or traction allays pain, lessens the danger of shock and avoids further trauma.

A plea is made for the immediate, careful and expert handling of compound fractures.

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A REVIEW OF UROLOGIC SURGERY

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KIDNEY

Tumor.—Droschl¹ reviewed the results of treatment in 66 cases of tumor (hypernephroid) of the kidney from the surgical clinic at Graz, Austria. He described in detail the symptoms, diagnosis and treatment. The treatment was always surgical. The results were poor. He agreed with the statement of Wildbolz that three years after the operation only a third of the patients with such a tumor are still alive. Droschl expressed the opinion that hypernephroid tumor is of a higher grade of malignancy than carcinoma or sarcoma.

Delon² reviewed the embryology of the kidney and the various hypotheses that have been advanced concerning the pathogenesis of renal tumor in children. These hypotheses fall into three groups, namely: (1) that such a tumor in children is of embryonal origin, (2) that it is caused by various inclusions, such as the wolffian body, myotoma and mesoderm, and (3) that it results from an "illegal union" between the metanephros

1. Droschl, Hans: *Ergebnisse der Behandlung von hypernephroiden Tumoren*, Ztschr. f. urol. Chir. u. Gynäk. **42**:206-221 (May) 1936.

2. Delon, Jeanne: *Tumeurs malignes du rein chez l'enfant: Etude anatomoclinique*, Arch. d. mal. d. reins **9**:655-692 (Nov.) 1936.

and the adjacent tissues. When a section taken from the peripheral region of the fetal kidney is compared with a section from a tumor, the similarity is striking. In both cases undifferentiated cells are seen in the process of transformation into connective tissue and epithelial cells. In the fetal kidney this transformation is perfect and regular; the epithelial cells become arranged in renal buttons, secretory tubules and glomeruli, whereas the connective tissue cells form the interstitial tissue. In the renal tumor this transformation remains incomplete and becomes clearly malignant. The epithelial cells proliferate much more actively than in the normal kidney. They reveal abnormal mitosis, and their structural evolution remains imperfect. They may be in masses without any apparent order, or they may be arranged like the renal buttons of the embryonic kidney; the formation of tubules is rare, and these, when present, are definitely neoplastic and are not confined to a single basal layer but possess several layers of cells and seldom present a central lumen. Glomeruli are altogether exceptional. The connective tissue cells also proliferate more actively than in the normal kidney and are characterized by various anomalies. They show various stages in the evolution of adult fibroblasts and a tendency to form collagen. This is never present in any significant amount in the normal kidney.

These epithelial and connective tissue modifications are the essential factor in the renal tumor in childhood. They are very simply explained on an embryologic basis. The tumor is the malignant degeneration of the nephrogenic tissue. Smooth muscle fibers are occasionally observed. In the normal kidney these are found in the hilar region; they extend into the ureter and sometimes even become insinuated between the lobes of the kidney; they also exist beneath the renal capsule. Hence their presence in a tumor should not occasion any astonishment and is as logical as the presence of epithelial or connective tissues. Cartilage and bone are rarely present, but when present they always appear in the middle of dense connective tissue abounding in collagen. As is well known, these are classified as connective tissues, and their presence is very simply explained by metaplasia. The interpretation of striped muscle fibers is certainly more difficult. Only once has the author found these, and then they were mingled with undifferentiated cells and fibroblasts, from the former of which they appear to be derived. The theory of inclusions and of "illegal union" is rejected by Delon, and the embryonal theory of Maus and Busse is accepted without reservation. The terms "malignant dysembryoma" and "malignant embryonal nephroma" seem to her the best designations.

In considering the genesis of the kidney, it has been pointed out that the development of the secretory portion does not take place when the ureteral bud is imperfect or when there is any arrest or modifi-

cation in the migration of the germinal cells. When such an arrest of development occurs, it gives rise to a malformation, but it does not explain a neoplasm. Some authors think, however, that the malformation causes malignant degeneration; but one could just as easily hold that it is malignant degeneration that causes an arrest of development. These are only hypotheses, which can neither be affirmed nor denied at present. The ultimate cause of malignant tumor of the kidney in children, like that of all forms of carcinoma, still eludes investigators.

Anomalies.—Everett³ reported in detail a case of complete unilateral reduplication of the renal pelvis and ureter. The symptoms, complicating pathologic changes and treatment in 48 other cases presenting similar anomalies were tabulated and discussed. A special study of the differential function of the various renal segments was made, and the conclusion was drawn that in the absence of serious complicating pathologic lesions the function of the two kidneys is usually about equal; on the side on which the reduplicated organs are present the function of the lower segment usually exceeds that of the upper segment in the ratio of about 2:1. Attention is called to the value of ureteral dilation as a conservative measure in the treatment of persons in whom pathologic changes have developed and to its possible rôle in the reduction of the incidence of operative treatment.

Stone.—Randall⁴ reviewed the five theories which are current today as reasons why a kidney becomes encumbered with a calculus and at the same time pointed out the close relationship of these theories.

Priority belongs to the dietary theory. Attention is called to this causal factor from two separate angles. First, and perhaps of the greatest importance, is the realization that the occurrence of vesical stone in childhood has almost disappeared. In former years stone in the urinary tract of children was common. Now it is rare, and the only factor which can be pointed out as bearing on the disappearance of this surgical condition has been a liberalization of the diet of children. Children today are fed from infancy a diet which would have made our grandparents shudder. The second point under this theory has been the proof that diets deficient in vitamin A are exceedingly prolific in the formation of calculus. The reason given is that such a diet causes certain changes in the epithelium of the urinary tract, which is termed keratinization. Two factors are significant: first, that such stones are consistently formed of calcium and magnesium phosphates, and second,

3. Everett, H. S.: Reduplication of the Renal Pelvis and Ureter, *J. Urol.* **36**:1-21 (July) 1936.

4. Randall, Alexander: An Hypothesis for the Origin of Renal Calculus, *Tr. New England Branch Am. Urol. A.*, 1935, pt. 3, pp. 6-22; *New England J. Med.* **214**:234 (Feb. 6) 1936.

that in experimental animals in which stone has been so produced such concretions have been made to disappear if the diet is changed to one rich in vitamin A.

The second theory which enters this picture is that of infection. Again, two factors are of great significance as regards infection and stone: first, the concomitant frequency of infection when epithelial changes due to deficiency of vitamin A predominate, with the interrelationship of these two theories; and second, the part that infection frequently plays as an etiologic factor in the recurrence of renal stone.

The third theory concerns the effect of stasis and faulty drainage. Long recognized factors in the formation of stone in the lower part of the urinary tract, stasis and faulty drainage must likewise play a definite part in the etiology of certain stones in the upper part of the urinary tract. Stone has been found in a relatively high percentage of patients who have been bedridden because of generalized disease, immobilization for fractured bones and tuberculous lesions of the hip and spine.

The fourth theory is one of disturbance in the colloidal mechanism of the urine, which plays an important part in the body's normal ability to eliminate insoluble crystalloids in a supersaturated solution in the urine.

The fifth theory is of recent origin; in this, it has been pointed out that hyperplastic disease of the parathyroid glands is responsible for decalcification of the bony skeleton and the occurrence of an actual calcium diabetes in the urine.

Kimbrough⁵ stated that all calculi of the urogenital tract should be removed as soon as the condition of the patient will warrant. There are no silent stones, and delay in removal is always dangerous. The type of operation that will cause the minimal amount of renal injury should be employed. Posterior pelviolithotomy is the operation of choice unless conditions make other procedures advisable. Repeated attempts at removal of ureteral calculi by manipulation may become a hazardous procedure, and persistence in this method of treatment is not commendable. Operation for ureteral calculi rarely causes morbidity. Drainage by means of nephrostomy has given good results when stones were present in association with severe renal infection, hydronephrosis and ureteral obstruction. The gastro-intestinal symptoms of urinary calculus merit important consideration. Each case in which stones are bilateral must be considered on its own merits; no fixed rule can be followed. The side on which the most acute symptoms are present or which reveals evidence of obstruction usually should be operated on

5. Kimbrough, J. C.: The Treatment of Urinary Lithiasis, *J. Urol.* 36:57-70 (July) 1936.

first. Other things being equal, the first operation should be done on the better kidney. If a patient has both renal and ureteral calculi, it is advisable to remove the ureteral stones before operating on the kidney. In the treatment of calculus of the urogenital tract, the high incidence of recurrence makes the conservation of renal tissue imperative. Nephrectomy should be performed only as the last resort. Renal sympathectomy is an important procedure in the operative treatment. The removal of the calculus is only a phase in the treatment of urinary lithiasis. Adequate postoperative care is necessary to reduce the incidence of recurrence and to prevent morbidity.

Higgins⁶ reported that he secured the following results by the use of the acid ash diet high in vitamin A in the treatment of urinary calculi.

In his series of 23 cases in which stones were too large to pass spontaneously from the kidney, the diet brought complete solution, as indicated by roentgenographic studies and by pyelography.

In another group of 17 patients calculi were passed at frequent intervals. After the acid ash diet high in vitamin A had been followed, all the patients were entirely free from symptoms for more than two years.

During the past two and a half years there was only 1 instance of recurrent formation of stone after operative removal of stones from the upper part of the urinary tract. This patient did not follow the routine that was outlined for him. Higgins does not wish to infer that, postoperatively, only the acid ash diet high in vitamin A was used. This was prescribed in addition to other therapeutic measures that he always has used, such as eradication of infection and elimination of stasis. Since this regimen has been followed, the incidence of recurrent formation of stone has been reduced from 16.4 to 4.7 per cent in his cases.

He also has studied a series of cases in which the stones have diminished in size, but insufficient time has elapsed to expect their complete solution.

In other cases he has been unable as yet to note any decrease in the size of the calculi, although the patients have followed the diet for a period of from four to five months. He stated that it was impossible to determine whether a noticeable decrease in the size of stones will occur after the diet has been followed for longer periods. He does believe, however, that if the stone is not producing definite renal injury and is not disabling the patient from pain, conservative treatment should be attempted.

6. Higgins, C. C.: *Experimental and Clinical Observations on Urinary Calculi*, Tr. New England Branch Am. Urol. A., 1935, pt. 2, pp. 6-17; New England J. Med. **213**:1007 (Nov. 21) 1935.

He is certain that if in addition to the other therapeutic measures which have been used previously a carefully planned diet is prescribed to which vitamin A is added postoperatively, the recurrent formation of stones can be reduced to a minimum.

Higgins⁷ stated that recurrent renal lithiasis, or the formation of a calculus after complete removal of the original stone, may be classed as a true recurrence and the persistence of stones or fragments of calculi which were overlooked at operation, as a false recurrence. Whether the type of stone is single or multiple, soft or hard, influences the tendency to recurrence. In Higgins' series of cases of renal calculi, those which were soft recurred more frequently. This may have been due to the retention of small fragments of sand in the kidney which acted as a nucleus for the further formation of stone. The postoperative results when bilateral calculi are present are not satisfactory from the point of view of recurrence. Bilateral infection of the urinary tract is present in a large percentage of cases, and this persists after operation. Recurrence usually follows the removal of bilateral calculi.

In recent years there has been a progressive tendency toward conservatism in operations for renal conditions. Pelviolithotomy was used in more than 74 per cent of Higgins' cases and is the procedure of choice for the removal of calculi from the renal pelvis, except when more extensive operation is required. Since trauma is minimized, recurrences seem less likely than when more extensive procedures are required. Nephrolithotomy may be necessary when a calculus is branched or is confined to a calix associated with a narrow infundibulum. This method should always be as conservative as possible, and often a small incision over the dilated calix is sufficient. Heminephrectomy may be indicated in the presence of marked dilatation of a calix in which severe infection is localized at the site of the stone. Nephropelviolithotomy may occasionally be required when technical difficulties arise or when drainage with a nephrotomy tube is desired. When this is used, the finger in the pelvis serves as a guide for the accurate placing of the tube.

In considering the postoperative management of the patient from whom a calculus has been removed by surgical intervention, various factors associated with the formation of stone must be considered. Infection may be divided into the focal type and that confined to the genito-urinary tract. When infection is present in the genito-urinary tract, a complete study of the causative organism is required, and it should be ascertained whether it has the urea-splitting property. If a colon bacillus or a mild staphylococcic infection is present in the kidney, conservative treatment with urinary antiseptics, such as ammonium

7. Higgins, C. C.: Prevention of Recurrent Renal Calculi, *J Urol.* **35**:494-498 (May) 1936.

chloride and methenamine, should be employed. If, however, the infection cannot be eradicated by this procedure, a ketogenic diet should be used. Urosthesis also seems to be associated with the recurrent formation of lithiasis. If stasis is present, it must be eliminated by dilation of the ureters or other required procedures. Higgins expressed the belief that vitamin A should be prescribed postoperatively to overcome any deficiency in this vitamin and because of its specific effect on the epithelial structures. In a few cases in which microscopic examination was made of a small piece of the pelvis of the kidney adjacent to a calculus, complete loss of epithelium has been found, which probably was caused by constant trauma by the calculus, and small accumulations of sand were found to be adherent at this point. Later, the calculus may become enlarged and then pass spontaneously down the ureter or fall into the dependent lower calix, affording a nucleus for further development of the stone. Because of the healing effect of vitamin A on the epithelium, this vitamin therefore is of value in promoting more rapid epithelization at the sites where the denudation has occurred. In a recent series of 43 cases of renal lithiasis, Jeans' test for deficiency of vitamin A was positive in 52 per cent. The relationship between hyperparathyroidism and renal lithiasis must also be considered. If hyperparathyroidism is present, exploration of the parathyroid glands is indicated, and the removal of a tumor of this gland will prevent recurrence of the calculi which were due to hyperparathyroidism. In view of the experimental evidence, Higgins expressed the belief that the recurrent formation of calculi could be minimized by the use of dietary treatment in addition to the other therapeutic procedures that have been used postoperatively in the past. The patient with calculi which are composed of calcium and magnesium phosphates, or carbonates, which form in an alkaline urine, or oxalates, which are precipitated in a wide range of urinary reactions, should be placed on an acid ash diet high in vitamin A after operation, thus shifting the urinary reaction to the acid side. When the calculi are composed of cystine or uric acid, the p_H should be shifted to the alkaline side by the use of an alkaline ash diet high in vitamin A after it is ascertained that phosphates and carbonate are not being precipitated at that degree of alkalinity. Vitamin A should be given in the form of capsules of halibut liver oil or carotene in oil, and Jeans' test should be rechecked to make certain that adequate amounts have been prescribed. In Higgins' experience, recurrent calculi are composed chiefly of calcium and magnesium phosphates, carbonates and traces of oxalates. These calculi form in an alkaline urine, and by shifting the reaction of the urine to the acid side, their recurrence should be minimized. Since the dietary regimen has been added to the postoperative treatment, the incidence of recurrent

renal lithiasis has been reduced from 16.4 to 4.7 per cent during the past three years.

Hydronephrosis.—Henninger and Sitka⁸ confirmed the experiments of Enderlen and others that urine from the hydronephrotic kidney is less toxic than normal urine. In a series of experiments they removed both kidneys of rabbits and found that the rabbits died from fifty to eighty hours later. Rabbits lived twice as long when both ureters were tied and the kidneys were left intact. To prove the toxicity of normal urine, they opened the ureter in the retroperitoneal space of 10 rabbits. Three animals died from fifty to one hundred hours later. A space filled with urine was found beside the normal kidneys. Seven animals survived the operation and were killed later. It was found that the opening in the ureter had closed and that hydronephrosis had formed above.

When the ureter had been ligated before being cut, so that hydronephrosis developed, the rabbits survived the operation, even when the incision in the ureter was kept open by a drain. This suggests that although normal urine usually kills a rabbit by resorption, urine from a nephrotic kidney never does.

The authors found the same adhesive tendency in the bladder that they had found in the course of their experiments on the ureter. When half of the bladder had been resected and left open to the peritoneum, it was closed in a few hours by the intestines, before peritonitis developed. The rabbits always survived the operation, and the bladder went on functioning normally.

Berkman⁹ drew attention to a group of patients who have hydronephrosis that is often unrecognized or misdiagnosed. These patients complain of attacks of pain in the upper part of the abdomen on one side or the other. Urinalysis, studies of renal function and a plain roentgenogram of the urinary tract reveal nothing abnormal. An important clinical clue in the detection of the hydronephrosis is obtained by determining the relationship of the pain to the posture of the patient. Pain occurs most frequently after exercise or toward the end of the day, when the patient has been erect for some time. Considerable relief is usually obtained by lying down, on the back, on the affected side or on the unaffected side. When such a history is elicited, one's suspicion of the possibility of hydronephrosis should be aroused, especially

8. Henninger, H., and Sitka, B.: Experimentelle Untersuchungen über die Toxizität des normalen und Hydronephrosenharnes bei Kaninchen und Mitteilung von Befunden einer merkwürdigen Verklebungstendenz innerhalb des Kaninchenharntraktes, *Ztschr. f. urol. Chir. u. Gynäk.* **42**:101-114 (Feb.) 1936.

9. Berkman, J. M.: Further Observations on the "Position-Relief Syndrome" in Hydronephrosis, *Proc. Staff Meet., Mayo Clin.* **11**:331-333 (May 20) 1936.

when examinations of other organs give negative results. Intravenous urography usually reveals the true diagnosis if renal function is not too seriously impaired. Surgical treatment is then generally indicated, and this usually consists of a conservative type of operation on the kidney, pelvis or upper portion of the ureter.

Trauma.—Dósza¹⁰ reported 83 cases of injury to the kidneys, in 67 of which the trauma was the result of direct violence. Hematuria was present in 65 patients. Conservative treatment was satisfactory for 79, and operation was performed on 3. One patient, who came to the clinic five days after the injury, died before operation could be performed.

Twenty-seven patients were seen from six months to thirty years after the initial injury and had to be operated on for various consequences of the renal injury. Hydronephrosis was present in 6, renal stones in 9, tuberculosis of the kidney in 10 and renal tumors in 2.

In some cases no association with the injury was demonstrable. In 2 cases the tumors were present before the accident. In several cases in which stones were present the connection could not be proved but was probable.

In cases of tuberculosis there are two possibilities which may arise after injury to the kidney: (1) The injury may make a preexistent tuberculous infection more obvious, and (2) it can send tubercle bacilli from distant infected areas to the injured kidney, which after the injury has a lowered resistance.

Dósza found that nephritis developed following an accident in 2 cases. He believed that in those cases the accident was really the principal etiologic factor and that the diagnosis was traumatic nephritis.

Findlay¹¹ stated that the mortality from rupture of the kidney continues to be high, and the lesion too frequently escapes prompt diagnosis. Not only is the injury to the kidney serious in itself, but it is frequently accompanied by other injuries of the thorax and abdomen, which require the best surgical judgment. Slight bleeding from the kidney may result from mild indirect trauma, such as a blow on the buttocks or a fall; actual rupture of the kidney is usually attributable to a direct blow over the kidney itself. Rupture caused by direct violence may be due to a rapid impact or to slow compression, the kidney being forced against the vertebral column or lower ribs. Mild trauma may result only in bruising of the kidney, with slight swelling and extravasation of blood. In true rupture of the kidney there are numer-

10. Dósza, Eugen: Ueber die subcutanen Nierenverletzungen und deren Spätfolgen, *Ztschr. f. urol. Chir. u. Gynäk.* **42**:222-230 (May) 1936.

11. Findlay, F. M.: The Treatment of Ruptured Kidney, with Case Report, *West. J. Surg.* **44**:117-121 (Feb.) 1936.

ous fissures which vary in extent and depth. If the pelvis of the kidney is involved, urine escapes into the surrounding tissues. If the renal artery or vein or one of their major branches is torn across, there is a prompt hemorrhage, with formation of a retroperitoneal tumor, a drop in blood pressure, pallor and all of the typical symptoms of shock. More frequently the injury consists of transverse rupture of the cortex, with the escape of blood but of only a small amount of urine into the surrounding tissues. Extravasation of a small amount of sterile urine rarely causes sepsis.

A problem of diagnosis arises when the kidney is known to be ruptured and the patient also has multiple injuries. The more common injuries are fracture of the ribs with pleural effusion, rupture of the spleen or liver and perforation of the intestine.

Analysis of the reported deaths in any series of injuries to the kidney reveals that surgical shock is the most common cause of death. Hemorrhage is one of the main causes of surgical shock.

Infection.—Von Illyés¹² reviewed the subject of suppuration of the renal parenchyma without taking into consideration the etiology, the diseases or the anatomic alterations which may have preceded the formation of pus. All forms of suppurative inflammation which have been caused by pyogenous bacteria are considered, with the exception of tuberculosis. All suppurations of the kidney that originate from general or local infections transmitted by the hematogenous or the lymphogenous route and infections following urinary diseases or arising from anatomic changes are also considered.

With regard to the pathogenesis, and from a point of view of systematic classification, von Illyés expressed the belief that it is simplest to suppose that the infections are of the following types: hematogenous, or descending; urogenous, or ascending, and lymphogenous. It is known that often neither surgical exploration nor postmortem examination will inform the physician how the infection has started; so the condition cannot be classified.

In hematogenous infection the capillary blood vessels of the glomeruli are obstructed by the bacteria invading the renal blood vessels, and local suppuration sets in. In other cases single germs permeate the canaliculi, reaching the medullary substance where they provoke abscesses.

Concerning excretion or metastatic abscesses, a larger number of germs or necrotic small particles of tissue may obstruct larger vessels, thus causing an infarct, which may decay through infection.

12. von Illyés, Géza: Ueber die Eiterungen des Nierenparenchyms, Kong. internat. Gesellsch. f. Urol., 1936, pp. 246-286.

In urogenous infection the lower part of the urinary tract is usually already infected. From there, infection ascends to the kidney, where urinary retention favors the development of infection. Bacteria reach the parenchyma by an antiperistaltic movement of the ureters or reaches the pelvis of the kidney by vesico-ureteral reflux; from thence they enter the kidney. By pyelovenous or pyelotubular reflux, more frequently even by pyelo-interstitial reflux, they travel as far as under the capsule or into the cortical substance, where they create small, purulent foci. Small interstitial abscesses such as these may break into the canaliculi, from whence they reach the medullary substance, presenting the same picture as if hematogenous infection, passing from the glomeruli into the canaliculi, had taken place. As the pelvis is always affected in such cases, this kind of inflammation is called pyelonephritis.

The lymphogenous etiology of renal infection can be ascertained in rare cases only. The infection following appendicitis or infections of the female adnexa may reach the kidney by way of the lymphatics in the walls of the ureter. Colon bacilli are the organisms most frequently found, but staphylococci and streptococci and other pyogenous germs also are found.

Clinically, three types of infection are distinguished: (1) suppurative nephritis, consisting of (a) circumscribed or scattered minor or major abscesses and (b) abscess of the kidney; (2) suppurative pyelonephritis, and (3) pyonephrosis, or shrinking kidney.

The hematogenous (descending) less often the urogenous (ascending) renal suppurations belong to the first group. These reveal minor or major, scattered or circumscribed and cortical or medullary abscesses. A special form of hematogenous infection, the carbuncle of the kidney, is included by von Illyés in this group. The term nephritis indicates mainly hematogenous renal suppurations. The second group is the largest and includes the various suppurations, mostly urogenous, that follow urinary diseases of different kinds. The term pyelonephritis indicates the origin from the pelvis or the urogenous (ascending) pathway of infection. The third group includes all the final results of suppurations. In this group the kidney is already destroyed but still causes symptoms that necessitate surgical intervention.

Cabot¹³ considered blood-borne infections of the kidney, chiefly those produced by the pus-producing cocci. For many years it has been known that various forms of these cocci may be found in the otherwise normal urine of patients who have peripheral infections, such as boils, carbuncles, septic wounds and acute infections of the upper part of the respiratory tract. In order to study the latter point more closely, a series

13. Cabot, Hugh: Blood Stream Infections of the Kidney. *Brit. J. Urol.* 8:233-256 (Sept.) 1936.

of 46 patients suffering from acute inflammatory processes about the mouth, throat and ear were studied. The group was selected from among patients who had a urine normal to ordinary tests and some fever, but revealed no signs or symptoms suggesting an infection of the kidney. The urine was carefully obtained, always by catheter from the females. It was studied by smear and culture, the smear being made from urine centrifugated for a considerable period at high speed. Of these 46 cases, organisms from 32 were revealed in the smear and from 18 in the culture.

It is important to note that the pus-producing cocci appear in the urine early in the disease, but disappear as a rule in a few days, although occasionally they may persist for several weeks in an otherwise normal urine.

The lesions are primarily cortical or medullary. They tend to coalesce with the production of a massive abscess and usually show early and marked perinephritis, often developing into a perinephritic abscess.

Besides the classic methods of diagnosis, stress is laid on the value of roentgenography in the diagnosis in these cases. In cases of perinephritic abscess clouding or obliteration of the shadow of the psoas muscle is generally revealed by modern methods of roentgenography. Scoliosis is not rare but is a rather late sign. Limitation of motion of the diaphragm on the infected side, as studied by the fluoroscope, is more important than the literature would suggest. Particular emphasis is laid on the value of pyelography, both by the excretory and by the retrograde method. This will give precise information as to the development of massive abscess by revealing deformities of the calices. It will also be of much value in showing displacement of the kidney by a perinephritic abscess, sometimes at an early period. Stress is laid on the value of limitation of the normal mobility of the kidney caused by the early development of perinephritis, often in the absence of a perinephritic abscess. A series of observations is reported, showing diminished visualization of the infected kidney as seen in the excretory urogram.

For the purposes of treatment, the infections are divided into four groups.

1. Fulminating infection. Operation is believed to be the only available method of treatment for this type.

2. Acute infection, the condition being characterized by chills, high fever, leukocytosis and costomuscular tenderness in association with a normal urine, except for the practically universal presence of cocci obtained by staining the sediment after prolonged centrifugation at high speed. For this type of infection operation has been generally

regarded as almost invariably necessary. Cabot was not in agreement with this opinion and expressed the belief that in a majority of cases recovery will take place if the patient is treated medically. A position of "armed watchfulness" should always be maintained, the reaction of the patient to the disease being carefully observed, particularly with regard to the tendency of the pulse to become more rapid and of anemia to develop. Coupled with this should be frequent observations of the conformation of the renal pelvis both by the excretory urogram and by the retrograde pyelogram. This will enable massive abscess and perinephritic abscess to be discovered early.

3. Subacute infection, the picture being less stormy, but presenting clear evidence of a lesion of the kidney. For this type of infection operation is not indicated, except when perinephritic abscess develops.

4. Infections of the borderline type which occur not rarely as a complication of infections of the upper respiratory passages, the diagnosis being made only on the basis of a slight costomuscular tenderness, the presence of fever which is not satisfactorily accounted for by the conditions in the throat and by the finding of cocci in the urine, as previously described. For this type of infection operation is practically never necessary, since perinephritic abscess is uncommon.

Cabot gave the following indications for operation: (1) the fulminating type of infection; (2) the widespread infection of the kidney in which the patient seems unable to control the disease, as may be noted by the development of anemia and failing general condition; (3) massive abscess of the kidney, as shown by the pyelogram, and (4) perinephritic abscess.

The following types of operation are indicated: (1) nephrectomy for the fulminating infections; (2) nephrectomy for widespread infection, but when massive abscess is not present and the patient is losing ground; (3) decapsulation and drainage for the well localized massive abscess, and (4) exploration for the perinephritic abscess. The precise operation for the perinephritic abscess is determined by the following factors: (a) If the pyelogram shows no evidence of massive abscess or evidence of deformity of the pelvis, simple drainage is employed. (b) If there is perinephritic abscess and evidence of massive abscess, the perinephritic abscess must be drained and the kidney explored in the region indicated by the pyelogram. (c) For perinephritic abscess of long standing, even with evidence of destruction of renal tissue, as shown by the pyelogram, drainage of the perinephritic abscess alone is indicated in the first instance. Many of the patients will then recover, since the massive destruction of the kidney has already drained into the perinephritic space. It is not wise to uncover the kidney widely in these cases, since extensive dissection will be necessary with the break-

ing down of well established barriers. If the perinephritic abscess has been drained, and the wound fails to heal or after healing reopens, further exploration can be safely undertaken.

Necker¹⁴ stated that suppuration of the parenchyma, in a wider meaning of the term, is the pathologic result of all nonspecific renal infections. He reviewed abscess-like suppurations of the kidney and divided them into two groups. The first group included all forms of suppuration limited to the parenchyma itself, namely, primary suppurations of the parenchyma. These forms of suppuration are still insufficiently studied and diagnosed with difficulty only; therefore, mainly the first group will be considered. The second group of suppurations is easier to diagnose clinically and is more frequently found; namely, secondary pyelonephritic or pyelorenal suppurations of the parenchyma in which the urinary excretory pathways are always involved.

Primary suppuration of the parenchyma is seldom diffuse; more often it is a sharply circumscribed disease of the cortex of the kidney. The organisms are pyogenous cocci and *Staphylococcus aureus* but rarely streptococci. The infection usually starts from suppurative foci in the peripheral zone. The morphology and the extension of the focus of infection depend on the quantity and the virulence of the invading bacteria. Forms of clinical importance are: the rare, diffuse miliary abscess and infarction of the kidney, the grouped miliary abscess, the tumor-like, boil-like cortical suppuration, the large intrarenal abscess and the xantholipomatous staphylomycosis.

The participation of the cortical layers of the kidney in all forms of suppuration of the cortex proves the connection of the cortex with its coverings. It is impossible to distinguish clinically diseases of the adipose capsule, such as epinephritic abscess or fibrosclerotic epinephritis, from suppurations of the cortex, for frequently the former are manifested only by the latter.

Secondary suppuration of the parenchyma is usually caused by infection with colon bacillus. The infection spreads, also in cases of hematogenous infection, by ascending from the pelvis toward the cortex, after having gone through three phases: the issue of the bacteria out of the blood, their adherence to the renal parenchyma and their multiplication. This development is influenced by dynamic factors of the urinary ways (impediments or obstacles to the outflow). In case of infection by cocci, suppuration of the parenchyma is the primary condition of the diseased kidney, whereas in case of infection by colon bacillus, it is the final stage of the dissemination of the infection.

14. Necker, Friedrich: *Parenchymeiterungen der Niere*, Kong. internat. Gesellsch. f. Urol., 1936, pp. 299-358.

Intravenous and retrograde pyelography enables an accurate diagnosis to be made of the boil-like suppurations when the disease has provoked elongation and dislocation of the calices. The picture is similar to that of other strangulating processes, such as tumors, cysts or polycystic degeneration. In spite of the progress of the methods of examination, a diagnosis of cortical suppuration of the parenchyma can be based, after elimination of other possible disease, only on the septicopyemic aspect, the painfulness on pressure in the lumbar region and on the temperature. At present, a clinical classification of the various types of cortical suppurations of the parenchyma is not possible.

Therapeutically, the following rules can be established: Considering that primary cortical suppuration heals spontaneously by breaking into the urinary tract, by absorption or by cicatrization, a short period of observation and conservative treatment are always justified.

Conservative treatment should not be delayed. An early diagnosis and early exploratory operation and decapsulation are desirable before the adipose tissue is destroyed by suppurative processes and before surgical intervention is made difficult by fibrosclerotic alterations of the renal capsule. If diagnosed early, most of the cortical suppurations give gratifying results with conservative operative treatment. Decapsulation, incision or enucleation of the focus of disease, with subsequent antiseptic open treatment, will usually give good results.

In secondary suppuration of the parenchyma there are satisfactory diagnostic methods of securing accurate information as to the etiology and bacteriology and the function of both kidneys and their motor function. In many cases conservation of the kidney is prevented by the etiology of the disease (operative lesions of the ureters, after gynecological operations, extirpation of diverticula and resection of the bladder). In other cases treatment with an inlying catheter, cystotomy or permanent drainage of the ureter may sometimes cause improvement, even if the condition is very serious. Often complete failure of the latter measures to reduce the fever enables the diagnosis of isolated suppurative foci to be made. In such cases the kidney can be saved only rarely from total destruction by decortication, ureterolysis, incision of abscesses or temporary nephrostomy. If the functional condition of the second organ is satisfactory, nephrectomy alone is sometimes indicated.

Beer¹⁵ reviewed 61 cases of coccic infection of the renal cortex observed prior to 1926 and 43 more recent cases in which operation was performed. Men are more frequently affected than women, and the majority of patients are between the ages of 20 and 50. In 38 of 43 cases, *Staph. aureus* was noted in cultures of pus; in 3 cases there

15. Beer, Edwin: Coccic Infections of the Renal Cortex, *J. A. M. A.* **106**: 1063-1070 (March 28) 1936.

was mixed infection. In 32 cases there were perinephritis and perinephritic abscesses as well as cortical abscesses. In 9 cases the kidney was not exposed or visualized, according to the records. In 13 cases the cortical abscess was anterenal. A study of the blood cultures revealed staphylococcemia in 7 of the 26 cases studied in this manner.

As the features of the disease may vary from an acute fulminating process to that of a subacute or chronic septic condition, the clinical picture presented by this type of infection may be said to be protean in character. In the majority of cases the picture is typical and may easily be recognized. While the focus of pus is under the fibrous capsule of the kidney and therefore under tension, the symptoms may be marked. As the cortical abscess ruptures into the perinephrium and localizes in this fatty tissue, symptoms may subside temporarily, only to become more definite as tension develops in the perinephric space. When the perinephric abscess breaks through the fascia of Gerota, tension disappears and many of the symptoms temporarily abate. As pus ruptures downward and descends between the two leaves of Gerota's fascia toward the pelvis, the symptoms may subside until the reaction of the tissues encloses the accumulation of purulent material.

The disease is characterized by a rise in temperature with or without chills and with pain in one or both lumbar regions. On physical examination the kidney usually cannot be felt, but if palpable it may be movable. There is regularly a definite tenderness over the involved kidney. If the elevation of temperature continues, there is a continued loss of weight and progressive anemia. The patient appears to be suffering from septicemia. Leukocytosis is usually present while the patient has fever. Examination of the urine at this stage may reveal nothing of significance.

The clinical picture of the typical, acute condition, whether associated with bacteremia or not, should be recognized and surgical treatment by incision, drainage and decapsulation in situ should be carried out. If this is done, the wound should not be closed tightly, as it is likely to become infected from the staphylococcic pus. Adequate rubber dam in front and behind the decapsulated kidney should be left in place for drainage. Usually, if the abscess is thoroughly drained and does not involve the whole kidney, decapsulation is curative.

Tuberculosis.—Wildbolz¹⁶ stated that until recently it has been generally recognized that renal tuberculosis heals in only exceptionally rare instances. The studies of Medlar differ from this earlier opinion. He found areas of tuberculosis in the kidneys of patients who had died of pulmonary tuberculosis. These areas were mostly cicatrized and had

16. Wildbolz, Hans: Ueber die Möglichkeit einer Spontanheilung der Nierentuberkulose, *Ztschr. f. urol. Chir. u. Gynäk.* 42:257-267 (Aug.) 1936.

never caused symptoms during life. Clinical observations seemed to confirm Medlar's opinion that renal tuberculosis may heal in the early stages.

There has been considerable confusion in the American and European literature concerning renal tuberculosis. This is due mostly to the fact that the nomenclature in the different countries varies considerably. What is described as "the early stages of renal tuberculosis" in America is called by European authors "tuberculous nephritis," and the fibrous type is spoken of as indurative tuberculosis. Beginning caseation, even if it is slight, is spoken of as "caseate renal tuberculosis" in the United States, and it is judged incurable without operation. Considering the difference of nomenclature, there is no difference in the opinion of most American and European authors.

In the treatment of renal tuberculosis, Wildbolz agrees with American surgeons. He does not advise nephrectomy in cases of tuberculous nephritis. In 1,300 cases of renal tuberculosis in which the examination was made by Wildbolz, there were only 20 of this type. In 17 cases the kidney had to be removed later, and at this time caseous tuberculosis was found. In only 3 of the 1,300 cases did the tuberculosis appear to be healed without operation. A detailed description is given of 1 case of spontaneously healed renal tuberculosis in which necropsy was performed. This is the second case of this type described in the literature.

Wildbolz concluded that the new communications on the possibility of a spontaneous healing of renal tuberculosis do not permit a change in the indications on the operative treatment of this condition. Caseous renal tuberculosis practically never heals without operative intervention. Noncaseous renal tuberculosis appears to have some chance of healing without operation. These forms are difficult to distinguish from the caseous forms, although the triad of symptoms, namely, bacilluria, pyuria and lessened function of the kidney, strongly suggests the existence of caseous tuberculosis. Therefore, in Wildbolz' opinion, a unilateral occurrence of this group of symptoms is sufficient evidence to remove the infected kidney if the opposite kidney is functioning well. The diagnosis of noncaseous tuberculosis is permitted after a kidney excreting tubercle bacilli reveals no marked impairment of function and its urine does not contain pus cells. The possibility of a nonoperative cure exists in such cases, and an attempt in nonoperative treatment may be made, even though the infection is one sided. The patient with such an infection must remain under continuous observation. Nephrectomy will become urgent if marked impairment of function or pyuria is found in a kidney which has been excreting tubercle bacilli, or if even a small cavity is seen in the pyelogram.

Wyler¹⁷ reported the results of an experimental study on tuberculous bacilluria. After injection of a thin suspension of tuberculous bacilli (bovine type) into the renal artery of rabbits, the urine was examined continuously for three days. It was impossible to find tuberculous bacilli either in direct examination or by injection into a guinea-pig. Intravenous injection of dextrose causes polyuria. A suspension of tuberculous bacilli injected with the dextrose does not cause bacilluria.

Actinomycosis.—Kretschmer and Hibbs¹⁸ reported a case of actinomycosis of the kidney of a girl aged 10 years. A review of the literature revealed that only 3 cases of the disease have occurred in children.

Renal actinomycosis is probably never primary in the kidney. The persistence of a sinus after nephrectomy for a chronic suppurative process in the kidney, in which tuberculosis of the kidney has been ruled out, should make one suspect that the condition may be due to actinomycosis. Likewise, the presence of a persistent discharging sinus in other parts of the body should lead one to suspect that the renal lesion may be due to actinomycosis.

Cystic Disease.—Wells¹⁹ reported 2 cases of unilateral polycystic disease of the kidney and summarized the present conception of the etiology, pathology, diagnosis and treatment of polycystic kidney. The first patient was a man aged 40 who complained of renal colic on the left side. Retrograde pyelograms gave evidence of the typical changes of polycystic disease on the left and a normal right kidney. At operation on the left kidney the peritoneum was opened, and a normal right kidney was palpated. The left kidney was removed, and in addition to polycystic changes a large intracystic papilloma was found.

The second patient was a woman aged 22; an enlarged left kidney was found on general examination. Pyelograms revealed a large filling defect in the pelvis and the lower major calix, and a diagnosis of neoplasm was made. The pyelogram of the right kidney revealed a normal organ. At operation the left kidney was found to be polycystic; a normal right kidney was palpated transperitoneally, and the left kidney was removed on the presumption that there was a tumor in addition to the polycystic change. The filling defect was caused by a large cyst.

Wells contended that in these 2 cases in which the pyelogram was normal and there were no abnormal findings on transperitoneal palpa-

17. Wyler, J.: Experimenteller Beitrag zur Frage der tuberkulösen Bacillurie, Vorläufige Mitteilung, Ztschr. f. urol. Chir. u. Gynäk. 42:157-163 (Feb.) 1936.

18. Kretschmer, H. L., and Hibbs, W. G.: Actinomycosis of the Kidney in Infancy and Childhood, J. Urol. 36:123-138 (Aug.) 1936.

19. Wells, Charles: Polycystic and "Unilateral" Polycystic Kidney: A Review of the Literature and Two Cases. One with Intra-Cystic Papilloma, Brit. J. Urol. 8:22-35 (March) 1936.

tion of the opposite kidney, the assumption is reasonable that the disease is unilateral. Time alone will tell whether the normal kidney was potentially polycystic. However, in predominantly unilateral disease, nephrectomy is indicated when symptoms arise on the diseased side which demand intervention.

Wells stated that in certain cases in which the pyelogram of the opposite kidney is normal and the kidney is normal to palpation transperitoneally at operation, a "clinical" diagnosis of unilateral disease can safely be made. Several postmortem examinations have disclosed true unilateral disease.

Extreme conservatism, because of the belief held by the majority that the disease is always bilateral, has excluded many patients from the benefits of a well planned operation. Wells stated that provided careful functional studies have been done (1) operations other than on the kidneys may be undertaken with little increased risk as contrasted with operations on the normal subject and (2) operations on, or for the removal of, one kidney can be undertaken (*a*) without undue risk if the function of the other kidney is good and (*b*) with considerable, but not prohibitive, risk in cases of extreme urgency, even when the function of the other kidney is poor.

The indications of extreme urgency are: (1) severe infections or injury, (2) severe lumbar pain and (3) suspicion that a malignant condition is present.

The operations which may be carried out on the kidney itself are as follows: (1) Rovsing's puncture, by which many cysts are broken down; (2) the excision of some of the larger cysts, which is not a really practical procedure; (3) partial decapsulation (Marion); (4) drainage of the pelvis and/or the perirenal tissue; (5) nephrectomy, and, for statistical purposes, (6) exploration of the kidney with no further procedure. Rovsing's puncture reduces the size of the kidney and furnishes relief from pain, but secondary nephrectomy is often called for, especially in cases in which infection is present.

Urinary Lithiasis.—Barney and Mintz²⁰ reviewed the work done at the Massachusetts General Hospital on the relation of the parathyroid glands to urinary lithiasis. Determinations of blood calcium and phosphorus were made on 288 of the 340 patients who had urinary lithiasis, observed in that institution in the years 1933 to 1935, inclusive. In this manner 12 (4.16 per cent) cases of hyperparathyroidism were discovered. This brings the number of parathyroid tumors to 29; 20 of these were associated with renal calculi. Of these 29 cases, skeletal lesions (osteitis fibrosa) alone were observed in 5, lesions of the urinary tract alone in 13 and combined urinary and skeletal lesions in 11.

20. Barney, J. D., and Mintz, E. R.: The Relation of the Parathyroid Glands to Urinary Lithiasis, *Brit. J. Urol.* 8:36-44 (March) 1936.

In 8 cases of renal stone, in 6 of which the condition was bilateral, autemortem studies of the blood and postmortem studies of the parathyroid glands were made. The parathyroid glands were not diseased in any case, but the finding of normal amounts of calcium and phosphorus in the blood in the presence of normal parathyroid glands was confirmed. Because of the impression that renal calculosis in disease of the parathyroid glands is likely to be bilateral, 35 cases in which bilateral stones were present were carefully examined, and this assumption was not confirmed.

Special precautions must be taken to avoid contamination with calcium when taking blood for the determination of the calcium and phosphorus content, and the determination should be made only by a competent biochemist. More than 11 mg. of calcium per hundred cubic centimeters of blood and less than 3.5 mg. of phosphorus should arouse suspicion of parathyroid disease.

If there is only slight or moderate renal injury and no urgent necessity for removal of the stones, the parathyroid glands should be operated on first. Failure to correct the metabolic dysfunction first may result in reformation of the stones after their removal.

The readjustment of the calcium and phosphorus in the blood to normal amounts is rapid after removal of the parathyroid tumor. In Barney and Mintz' series of cases there has been no recurrence of stone, despite the fact that infection and obstruction persisted in a number of cases. However, the other important factors in the etiology of calculosis should not be neglected in the follow-up treatment. A careful dietary regimen should be planned; chemical examination of the blood and urine should be made frequently; the urine should be kept strongly acid, and roentgenograms of the urinary tract should be made from time to time.

Barney and Mintz concluded that no physical examination, especially if urinary lithiasis is present or suspected, is complete without a careful study of the calcium and the phosphorus content of the blood.

Pyelitis Cystica.—Hinman, Johnson and McCorkle²¹ stated that pyelitis and ureteritis cystica are pathologic conditions of the mucous membranes of the pelvis and ureter secondary to an inflammatory process. Cystitis cystica is almost always an associated condition. The mechanism of production is probably that described as the "cell nest" theory of von Brunn. The present methods of urologic study of pyelitis and ureteritis permit a clinical diagnosis of the condition in many cases. Dilatation of the ends of the major calices with narrowing of the arms of the calix below and cystic dilatation at the ureteropelvic junction

21. Hinman, Frank; Johnson, C. M., and McCorkle, J. H.: *Pyelitis and Ureteritis Cystica: Three Case Reports with Clinical Diagnosis*, J. Urol. **35**:174-189 (Feb.) 1936.

(not true pyelectasis) are typical of pyelitis cystica. The peculiar mottling of the ureterogram, similar to bubbles of air in the ureter, is typical of ureteritis cystica.

Physiology.—Pisani²² stated that the function of the kidneys is comprised of two distinct acts, namely, secretion and excretion. First, waste substances and varying amounts of water are filtered and secreted by the kidneys from the blood, and thus urine is formed. Second, the urine which has been formed is excreted through a system of communicating canals and cavities.

Urinary excretion is that physiologic function the purpose of which is to gather and evacuate the secreted urine. The apparatus which carries out this function starts at the apex of the calices, continues through the pelvic tract, the ureter, the bladder and the urethra and finishes at the external urethral meatus. A study of the pathologic changes of renal excretion involves consideration of all the urinary functional alterations that take place which disturb normal physiologic evacuation of the urine, from the calices through the pelvis and the ureter to the bladder.

If the renal excretory system can be divided into several segments (calices, pelvis and ureter) from an anatomic and topographic point of view, it physiologically and pathologically makes up one functional unit only; in pathologic conditions, any segmental alteration causes functional disturbance of all the apparatus.

Physiologically, the pyelo-ureteral system is equipped to carry out an important function of compensation in the changeable adaptations, which are ruled by the variations of secretory diuresis, and evacuation of the bladder. With a rapid increase of diuresis, or delayed evacuation of the bladder, it reacts with extra physiologic muscular movement and a lowered tonus; the object of this is to increase the capacity of the excretory ducts and the quantity of urine evacuated so as to keep an equilibrium between secretion and excretion. The pelvic cavity is the segment which contributes the most to this compensation by becoming dilated.

Any pathologic cause that undermines the functional integrity of the dynamic elements (muscular fibers, innervation centers and tracts) or hinders the free course of the urine in the inside of the excretory tracts becomes a factor in the lack of functional equilibrium. In these conditions the results may be different; the compensatory elements may succeed in restoring a normal function by doing away directly with the cause, they may keep up a relative equilibrium pending removal of

22. Pisani, G.: *Pathologia della escrezione renale*, Kong. internat. Gesellsch. f. Urol., 1936, pp. 380-472.

the cause or they may reach the state of total lack of compensation through a new primitive equilibrium obtained at the cost of greater functional activity.

The causes capable of producing a pathologic alteration of renal excretion are: (1) congenital malformations; (2) pathologic conditions of any kind, acquired or congenital and capable of contracting, occluding or compressing the caliber of the excretory ducts; (3) anatomic and functional lesions of the intrinsic or extrinsic muscles or nerves capable of stimulating, inhibiting, abolishing or in any way incoordinating the essential properties of tonus and motivity of the neuromuscular excretory system, and (4) congenital or acquired conditions which may influence the opening and closing of the ureteral outlets.

The causal anatomic and etiologic element can act pathogenically in causing a pathologic excretory lack of equilibrium only in two ways: (1) either as a mechanical irritating and transitory factor, capable of producing an exaggerated irritating dynamic reflex, or as an abnormal factor, in excess in the beginning and afterward in default, and (2) either as a first or as a second lesion factor of anatomic integrity of the neuromuscular system that rules renal excretion. In this case it is an essentially dynamic element. As the principal element of renal excretion is that of the peristaltic waves, it depends directly on the dynamic laws. The mechanical laws intervene only in special cases, by causing alterations that always end by having an echo in the dynamism of the pyelo-ureteral duct.

Fuchs²³ proved that the fornices of the calices of the kidney have a physiologic function. Rupture of the fornix and pyelovenous reflux are a pathologic event. Under physiologic conditions there is resorption through the fornix, not by rupture but by formation of small splits between the cells of the epithelium. Study of the ontogenesis reveals that the fornices have an important function. Reabsorption through the fornices is necessary to secure a proper balance between secretion and excretion of urine.

The morphologic changes the fornix undergoes in adapting its function to unusual demands is given as proof of the importance of the fornix.

Wildbolz and Walthard²⁴ examined 74 recently removed kidneys of human beings by the method of Warburg. They were able to measure

23. Fuchs, Felix: Die physiologische Rolle des Fornixapparates, *Ztschr. f. urol. Chir. u. Gynäk.* **42**:80-100 (Feb.) 1936.

24. Wildbolz, Hans, and Walthard, Bernhard: Die Beeinflussung der Funktion und des Stoffwechsels der Niere durch tuberkulöse und banale Infektion, Lithiasis, Harastauung und primäre maligne Tumoren, *Ztschr. f. urol. Chir. u. Gynäk.* **42**:1-20 (Feb.) 1936.

the respiration, that is, the consumption of oxygen, by the surviving animal tissue.

Sixty of the kidneys were tuberculous; 11 were hydronephrotic, some of which were the site of pyelonephritis and lithiasis, and 3 were the site of primary malignant tumors. The kidneys were removed with the patients under ether anesthesia. The most normal sections, while still warm, were placed in Ringer's solution and examined at once.

The authors compared the renal function before operation with the microscopic changes found and the metabolism of the parts of the kidney examined: In cases of caseating tuberculosis of the kidney, renal function and the consumption of oxygen were comparatively parallel. In cases of early tuberculous involvement in which normal tissue could be examined that was removed at a distance from the tuberculous focus, the metabolism was normal. In cases in which caseation was advanced and in which renal function was extensively injured, leaving only small areas of normal tissue, the microscopically normal areas had a highly reduced metabolism.

Wildbolz and Walthard concluded from this that the damaging effect of the tuberculous toxins extended for only a short distance around the focus and that in cases of early tuberculous involvement the tissue that is at a distance from the focus remains untouched. Acute inflammatory processes increase the consumption of oxygen.

Conclusions could not be drawn from the 3 cases of malignant tumors, but in all 3 the consumption of oxygen of the normal parts of the kidney was normal or slightly increased.

Sympathectomy.—Gibson²⁵ concluded that renal sympathectomy produces no harmful effects on the kidney; it is surgically feasible either alone or in conjunction with other procedures, and in a number of conditions there are either relative or definite indications for its application.

Among the indications for renal sympathectomy are renal sympatheticotonia (spasm, atony, dyskinesia, hyperdynamic motility and adynamia), either alone or in association with definite organic changes (slight hydronephrosis, nephroptosis, painful chronic nephritis, painful adhesive perinephritis, essential hematuria, certain types of Bright's disease associated with oliguria and anuria, cases of unyielding reflex anuria and possibly certain cases of stone-forming diathesis).

Renal sympathectomy is recommended, in conjunction with other necessary surgical procedures, as an extraprecautionary measure to make doubly sure of complete relief in any case of proved renal pain in which careful investigation reveals little or no demonstrable pathologic change to explain the symptoms adequately.

25. Gibson, T. E.: The Present Status of Renal Sympathectomy. California & West. Med. 45:10-13 (July) 1936.

Denervation.—Dambrin²⁶ expressed the belief that he was the first, in 1932, to envisage and carry out "total denervation" of the kidney, which included chemical sympathectomy of the renal pedicle and cortex after rapid denervation of the pedicle with the knife, and decapsulation. This total denervation frees the kidney by complete section of its nerves from the sympathetic centers and thereby prevents all vasoconstrictor action. It produces enormous vasodilatation. For a certain length of time the kidney becomes an organ controlled by its parasympathetic nervous system and no longer responds to the vasoconstrictor nerves, which predominate in the diseased kidney, nor does it react with any pain. Decapsulation alone and instrumental denervation alone are incomplete procedures. Dambrin supplemented these two procedures with *badigeonnage*, which is the application of Doppler's solution (a preparation of phenol) to both the decapsulated cortex and the renal pedicle.

Total denervation of the kidney is compatible with excellent secretory function of the organ. There is everything to indicate that intrarenal nerve centers exist which are adequate for the control of the phenomena of secretion. Since such centers have been discovered in the heart and intestine, it is the author's conviction that similar centers in the kidney will some day be brought to light. By suppressing the paths of conduction, this intervention acts on many a reflex anuria and has produced good results in nephralgia, hematuric nephritis and essential hypertension, in which the vasomotor factor was the most important.

Badigeonnage of the decapsulated kidney causes congestion of the gland and revitalization comparable to that which is known to occur in the testes and ovaries under this treatment. That it acts directly on the glomeruli and perhaps on the intrarenal nerve centers without doing the least injury to the normal formation of the kidney, has been shown indisputably by numerous histologic sections. The association of these three procedures gives more intense effects than any kind of partial action.

The operation is simple and is done in four stages: (1) decapsulation, (2) denudation of the artery and section of five or six large nerves surrounding the pedicle (small fibers may be disregarded); (3) *badigeonnage* of the artery and cortex with a gauze tampon soaked in the phenol solution, a substance without injurious effects, and (4) nephropexy, by any suitable method. In cases of nephritis in which the capsule is stoutly adherent and in which severe perinephritis renders

26. Dambrin, Louis: "L'énervation totale" du rein ou "sympathectomie chimique du pédicule rénal et de la corticalité du rein après énervation rapide du pédicule au bistouri et décapsulation," J. d'urol. 41:105-111 (Feb.) 1936.

decapsulation impossible, one may, if necessary, do simple *badigeonnage* without decapsulation. In this case the liquid acts on the nerves of the enveloping capsule and by destroying them prevents the vasoconstrictor action of the renocapsular anastomosis.

Indications for this treatment are found in painful conditions caused by slight hydronephrosis, compression of the kidney by the capsule, irritation of the renal plexus or neuritis and in certain cases of nephritis in which the normal cells of the kidney are only slightly involved and in which the majority of the disturbances are of a vasomotor nature. In cases of very acute nephritis, whether toxic or infectious, only mediocre results have been obtained. Chronic interstitial nephritis (Bright's disease) is hardly affected at all, but the operation is formally indicated in cases of hematuric nephritis. In cases of reflex anuria, total denervation should replace simple decapsulation. One of the best indications is found in cases of permanent hypertension, whether of glomerulonephritic or of nephro-angiosclerotic origin.

Dwarfism.—Kennedy²⁷ reviewed 7 cases of renal dwarfism and presented details of 5 of these cases. He emphasized the fact that the etiology, pathogenesis and relation of renal dwarfism to renal disease, hyperparathyroidism, other types of endocrinopathy and disturbed mineral metabolism are unknown. Clinically, the picture presented by these cases is that of retarded growth and skeletal development, changes in the roentgenographic appearance of the bones, impairment of renal function with resultant polyuria, polydipsia, albuminuria, azotemia and hyposthenuria, and hyperphosphatemia, with normal or abnormal concentrations of serum calcium. The changes in the skeleton which have been designated as renal rickets are sometimes striking features of the disease. Parsons has divided these changes into three types: (1) the atrophic type, in which the bones are fragile, atrophic and osteoporotic, with lines of cancellous tissue at the epiphysial ends of the diaphysis, a thin, atrophic cortex and fractures of the shaft; (2) the florid type, in which changes are characteristic of florid rickets, and (3) the woolly, stippled or honeycomb type, in which the epiphysial ends of the shaft are swollen and appear honeycombed, stippled or woolly. The ages of the patients ranged from 16 months to 8 years. Although in all the cases all the typical clinical findings were not present, retarded growth and development, impairment of renal function and some roentgenographic abnormalities were uniformly observed.

27. Kennedy, R. L. J.: Renal Dwarfism, Proc. Staff Meet., Mayo Clin. **11**: 289-293 (May 6) 1936.

URETER

Diverticulum.—Brown²⁸ stated that diverticulum of the ureter is rare and that the cases reported appear to belong in several different categories, which have not as yet been clearly defined. Diverticulum of the ureter may be divided into three different types. Diverticulitis of the ureter is an acquired form of diverticulum, caused by some inflammatory lesion which weakens the wall of the ureter, and a "blow-out" forms at the point of weakening. This may or may not be accompanied by the formation of stones in the ureter. Ureterocele is a type of diverticulum occurring as a dilation of the intramural portion of the ureter just proximal to the orifice of the ureter in the bladder. The opening of the ureter is constricted, and the cystic mass projects into the cavity of the bladder. Congenital diverticulum occurring along the course of the ureter is the rarest form of this type of lesion. Only 8 cases have been reported in the literature. Brown reported a ninth one. The etiologic factor in the causation of this type of diverticulum is evidently failure of a portion of the ureteral bud to join with its functioning cap.

Ureterocele.—Lazarus²⁹ stated that cystic dilatation of the lower end of the ureter, or ureterocele, more frequently accompanies anomalous conditions of the ureter and particularly supernumerary ureters. Although several hypotheses have been advanced to explain this entity, the one which appears most logical is that the dilatation is due to some type of obstruction at the ureteral orifice, along with a weakening of the tissues around the submucosal end of the affected ureter.

Symptoms attributable to ureterocele are dependent on (1) obstruction of one ureter in the event the cyst is confined to one meatus or of both ureters when the cyst is bilateral or obstructs the vesical neck and (2) cystitis.

The diagnosis of ureterocele is definitely made by cystoscopy, but it can be strongly suspected on the basis of the roentgenographic picture. The suggestive findings by excretory pyelography are: (1) dilatation of the lower 2 to 4 inches (5 to 10 cm.) of the ureter, (2) bulbous dilatation of the vesical end of the ureter and (3) a negative shadow or defect in the cystogram in the region of the bulbous end of the affected ureter.

The treatment of cystic dilatation of the lower end of the ureter consists of (1) transurethral methods, (2) intravesical methods and

28. Brown, Alfred: Ureteral Diverticula, *West. J. Surg.* **44**:270-278 (May) 1936.

29. Lazarus, J. A.: Cystic Dilatation of the Lower End of the Ureter: Special Reference to the Transurethral Treatment with the High Frequency Cutting Current; Report of Two Cases, *J. Urol.* **36**:139-149 (Aug.) 1936.

(3) nephrectomy when the kidney is destroyed. The procedure employed by the author was the use of the high frequency cutting current passed through a cystoscope by which the cyst was widely opened. Subsequent treatment consists of repeated dilation of the newly established ureteral orifice.

Lazarus reported 2 cases of cystic dilatation of the lower end of the ureter associated with reduplication of the pelvis, which have been completely relieved by the transurethral use of the high frequency cutting current.

Rhodes³⁰ reported 13 cases of ureterocele. Congenital stenosis of the orifice of the ureter is the most likely explanation for the lesion. Symptoms are mainly attributable to obstruction and infection. Diagnosis is made by cystoscopy and occasionally on the basis of the roentgenographic picture. The method of treatment advocated is the transurethral incision of the cyst by means of the diathermy current.

Changes in Pregnancy.—Traut and McLane³¹ stated that the normal ureter of the nonpregnant woman is possessed of rhythmic peristaltic activity which can be measured and recorded. This rhythmic peristaltic activity is definitely altered in varying degrees by pregnancy in the majority of the patients studied. There is diminished amplitude of the peristaltic wave; this commences in the third month of pregnancy and reaches its peak during the seventh and eighth months. After the fifth month the number of patients who had diminished ureteral response exceeded those who had normal activity. During the last month of pregnancy there seemed to be a definite return of muscular irritability, as expressed by the measurement of peristalsis and responses to stimulation. This diminished peristaltic activity of the ureters seen in pregnancy cannot be explained on the basis of dilatation. Dilatation of the ureters during pregnancy is probably mainly dependent on atony of the ureters. Traut and McLane expressed the belief that the etiology of this ureteral atony observed during pregnancy is not dependent on any mechanical factor but on some, as yet unexplained, chemical basis.

Stone.—Shaw³² reported 4 cases in which vaginal ureterolithotomy had been performed and which illustrate some of the advantages of this procedure. In 2 patients the operation seemed to be imperative, as removal of the calculus by any other approach appeared impossible at the time. The accidental production of vesicovaginal fistula in his

30. Rhodes, J. S.: The Clinical Importance of Ureterocele, *J. Urol.* **35**:300-308 (March) 1936.

31. Traut, H. F., and McLane, C. M.: Physiological Changes in the Ureter Associated with Pregnancy, *Surg., Gynec. & Obst.* **62**:65-72 (Jan.) 1936.

32. Shaw, E. C.: Vaginal Ureterolithotomy, *J. Urol.* **35**:289-297 (March) 1936.

first case revealed a possible operative complication. If the relationship of the base of the bladder, uterine cervix and ureter is borne in mind, this accident should never occur. The bladder can be readily avoided by inclining the dissecting finger laterally and posteriorly and approaching the ureter on its lateral and posterior aspect. A wound made in the ureter by this approach should be no more difficult to heal than one made in the more orthodox manner. The healing time in Shaw's cases was probably reduced by the employment of the indwelling ureteral catheter—a point, however, which can be settled only by more experience. Differences of opinion may arise as to the selection of cases for the employment of vaginal ureterolithotomy. Impacted stones, readily palpable on vaginal examination, fall into this group. Shaw has not used the operation for a calculus that was not palpable on vaginal examination, but it is probable that calculi so small or so high as not to be palpable, but demonstrated in the lower part of the ureter in the roentgenogram and fixed with a ureteral catheter, may be handled by this approach. The failure of an attempt to remove urinary calculus by the vaginal route would be of no particular danger to the patient, and it might be tried even in doubtful cases before abdominal operation is employed. The advantages of vaginal ureterolithotomy are that it is a comparatively simple method of removing a stone from a site which is often difficult to approach by other methods; it affords dependent drainage in case of leakage; it avoids an external incision, and it shortens the period of convalescence.

Tumor.—Jeck³³ reported a case of bilateral metastatic carcinoma of the ureters, which was probably true metastasis from a primary focus in the sigmoid colon, causing obstructive anuria. He also reported a case of adenocarcinoma of the kidney in which the diagnosis was made clinically and the kidney removed. The patient died as a result of a concealed hemorrhage, and necropsy revealed an adenocarcinoma of the opposite kidney, which was not recognized preoperatively.

Bilateral tumors of the ureter have received little or no attention clinically. It would seem, however, that anuria attributable to obstruction caused by bilateral tumor of the ureters, although rare, is sufficiently significant to warrant its consideration, especially in cases of obstructive anuria not caused by stone. Jeck's other case emphasized the fact that bilateral tumor of the kidneys may exist oftener than is supposed. More attention should be directed to the supposedly sound kidney in eliminating the possibility of malignant disease.

33. Jeck, H. S.: Bilateral Malignant Lesions of the Upper Urinary Tract: Case Reports, *J. Urol.* **35**:206-212 (Feb.) 1936.

Trauma.—Hryntschak³⁴ opposed the widespread belief that a ureter that has been sectioned transversely cannot resume its normal function. After reviewing the literature both on animal experimentation and on clinical work, he described his own experiments, indicating his results in the healing of the ureter after resection. He found that the resumption of normal function after transverse section of a ureter is physiologically possible. Complete restitution of nonstriated mucular fibers does not occur. The nerve impulses probably pass through a few regenerative muscular fibers that could be found in most postoperative scars.

Hryntschak expressed the belief that the two principal needs for healing of a transverse cut in the ureter are temporary diversion of the urine through nephrostomy, pyelostomy or ureterostomy and the splinting of the injured ureter with a ureteral catheter.

Anomaly.—Deming³⁵ stated that ectopic ureters of the vagina produce uniform symptoms of vaginal dripping of urine which exists with normal urination. The opening for this anomalous ureter is on the anterior wall of the vagina near the midline between the hymen and the cervix. The right side is the more often involved, and the ureter always extends to the upper pole of the kidney. The kidney attached to the ectopic ureter of the vagina is of practically no functional value and is prone to infection. Intravenous injections of skiodan may not be of value in the diagnosis. No attempt should be made to conserve such ureters and kidneys. Heminephrectomy may be done if vessels are distinct to each kidney. If infection is present, complete nephroureterectomy is indicated. Diagnosis should be made in the first decade of life. Total ureterectomy affords a simple method of treatment when infection has not taken place.

Crenshaw and Buchtel³⁶ reported 7 cases of ectopic ureter with an extravesical orifice. They stated that the choice of surgical procedure depended on the conditions in the individual case, namely, the situation of the ectopic ureteral orifice, the presence or absence of single or supernumerary ureters, the presence or absence of infection or pathologic changes in any segment of either kidney or ureter, the function of all segments of both kidneys, the difficulty of surgical renal approach and the distribution of the vascular supply to the two segments. Various surgical procedures may be employed that are suitable to the individual case. The ectopic ureter may be ligated either through the vagina or

34. Hryntschak, T.: Zur Histologie und Physiologie des querdurchtrennten Harnleiters, *Ztschr. f. urol. Chir. u. Gynäk.* 42:268-291 (Aug.) 1936.

35. Deming, C. L.: Ectopic Vaginal Ureter, *Surg., Gynec. & Obst.* 62:843-851 (May) 1936.

36. Crenshaw, J. L., and Buchtel, H. A.: Ectopic Ureter with Extravesical Orifice, *J. Urol.* 35:190-203 (Feb.) 1936.

at a point above the bladder. In 2 of their cases the ureter was ligated; 1 patient had a stormy convalescence; when 68 years of age she reported that she was well but had a cystic mass in the same side of the abdomen. The second patient recovered only after the drainage of a cystic kidney. An aberrant ureter may be transplanted into the bladder either through the vagina or transabdominally. In 2 of the cases this procedure was carried out transabdominally. One of the patients had a single aberrant ureter and had a satisfactory functioning and symptomless kidney eleven years after operation. The other patient had a small, uninfected upper segment and was perfectly well, with no change in function, ten months after operation. Heminephrectomy has its technical difficulties and may be precluded by inability to elevate the kidney or by the vascular distribution. In 1 case results were satisfactory after heminephrectomy. Nephrectomy may be indicated when both renal segments are pathologic or when other procedures fail, if the remaining kidney is normal. In 1 of the cases nephrectomy was performed with satisfactory results. Anastomosis, pelvis to pelvis, ureter to ureter or ureter to pelvis may be used. In suitable cases this should give good results and is a satisfactory method when other operations are not possible. An opening may be established between the ureter and the bladder by a plastic operation through the vagina, by cystotomy or by cauterization through the cystoscope.

(To be concluded)

PERITONITIS

I. THE EFFECT ON BLOOD PRESSURE OF THE PERITONEAL CONTENT IN SUPPURATIVE AND IN BILE PERITONITIS

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One of the common hypotheses of the cause of death from peritonitis is that of vasomotor collapse incident to the absorption of toxins from the peritoneum. It has long been assumed that causative micro-organisms have been the source of the toxins, with the peritoneum acting merely as an absorptive membrane of a large surface area. As early as 1902 certain authors,¹ on the basis of experimental results, advocated preliminary nonspecific irritation of the peritoneum to prevent the absorption of toxins. They believed that peritoneal absorption was retarded by a fibrinous exudate. The physiology of the peritoneum is now better understood. This knowledge has been reviewed by Cunningham² and by Livingston.³ Steinberg⁴ clarified the situation with a clearcut series of experiments in which the diphtheria bacillus was used

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1. Soleri, S.: Experimentelle Untersuchungen ueber die Veraenderungen des Widerstandes des Peritoneums gegen die Infection durch Bacterium Coli, Beitr. z. path. Anat. u. z. allg. Path. **31**:536, 1902. Miyake, H.: Experimentelle Studien zur Steigerung der Widerstandsfähigkeit der Gewebe gegen Infektion, Mitt. a. d. Grenzgeb. d. Med. u. Chir. **13**:719, 1904. Von Mikulicz, J.: Versuche ueber Resistenzvermehrung des Peritoneums gegen Infection bei Magen- und Daroperationen, Arch. f. klin. Chir. **73**:347, 1904. Von Graff, E.: Zur Behandlung von Laparotomien mit subkutaner Injektion von Nukleinsäure, Mitt. a. d. Grenzgeb. d. Med. u. Chir. **24**:466, 1912. Hoehne, O.: Ueber Toxinresorbtion aus der Bauchhöhle und ueber intraperitoneale Narkose, Zentralbl. f. Gynäk. **36**:258, 1912.

2. Cunningham, R. S.: Physiology of Serous Membranes, Physiol. Rev. **6**:271, 1926.

3. Livingston, E. M.: Clinical Study of the Abdominal Cavity and Peritoneum, New York, Paul B. Hoeber, Inc., 1932.

4. Steinberg, B.: The Cause of Death in Acute Diffuse Peritonitis, Arch. Surg. **23**:145 (July) 1931.

for intraperitoneal injection. While he found death to be due to the corresponding toxin, resistance was believed to be due to rapid phagocytosis, removing bacteria from the peritoneal cavity before the formation of a toxin could take place. This work, as well as the previous experiments of Gay and Morrison,⁵ has been the point of departure for immunization of the peritoneum.⁶

That there is a toxic substance involved in death from intestinal obstruction has long been believed, as a result of the work of Murphy and Brooks,⁷ Whipple, Stone and Bernheim,⁸ Dragstedt and his co-workers⁹ and others.¹⁰ Recently, Scott and Wangenstein¹¹ showed that the peritoneal fluid removed from dogs dying of experimental intestinal strangulation was nontoxic unless an intestinal loop was actually gangrenous. Since paralytic ileus is frequently associated with

5. Gay, F. P., and Morrison, L. F.: Clasmatoocytes and Resistance to Streptococcus Infection: V. Studies in Streptococcus Infection and Immunity, *J. Infect. Dis.* **33**:338, 1923.

6. Rankin, F. W., and Bagen, J. A.: Vaccination Against Peritonitis in Surgery of the Colon, *Arch. Surg.* **22**:98 (Jan.) 1931. Steinberg, B.: A Rapid Method of Protecting the Peritoneum Against Peritonitis, *ibid.* **24**:308 (Feb.) 1932. Herrmann, S. F.: Experimental Peritonitis and Peritoneal Immunity, *ibid.* **18**:2202 (April) 1929. Steinberg, B., and Goldblatt, H.: Protection of the Peritoneum Against Infection, *Surg., Gynec. & Obst.* **57**:15, 1933. Trenouth, A. M., and Bagen, J. A.: Peritoneal Reactions to Vaccine: Temperature Reactions After Intraperitoneal Vaccination, *Proc. Staff Meet., Mayo Clin.* **8**:583, 1933.

7. Murphy, F. T., and Brooks, B.: Intestinal Obstruction: An Experimental Study of the Cause of Symptoms and Death, *Arch. Int. Med.* **15**:392 (March) 1915.

8. Whipple, G. H.; Stone, H. B., and Bernheim, B. M.: Intestinal Obstruction, *J. Exper. Med.* **17**:286 and 307, 1913.

9. Dragstedt, L. R.; Moorhead, J. J., and Burcky, F. W.: The Nature of the Toxemia of Intestinal Obstruction, *Proc. Soc. Exper. Biol. & Med.* **14**:17, 1916; Intestinal Obstruction: An Experimental Study of the Intoxication in Closed Intestinal Loops, *J. Exper. Med.* **25**:421, 1917. Dragstedt, L. R.; Dragstedt, C. A.; McClintock, J. T., and Chase, C. S.: Intestinal Obstruction: II. A Study of the Factors Involved in the Production and Absorption of Toxic Materials from the Intestine, *ibid.* **30**:109, 1919.

10. Gerard, R. W.: The Lethal Agent in Acute Intestinal Obstruction, *J. A. M. A.* **79**:1581 (Nov. 4) 1922; Chemical Studies on Intestinal Intoxication, *J. Biol. Chem.* **52**:111, 1922. Foster, W. C., and Hausler, R. W.: Acute Intestinal Obstruction: III. Simple Obstruction, *Arch. Int. Med.* **36**:31 (July) 1925. Wangenstein, O. H., and Chunn, S. S.: Studies in Intestinal Obstruction: I. A Comparison of the Toxicity of Normal and Obstructed Intestinal Content, *Arch. Surg.* **16**:606 (Feb.) 1928. Wangenstein, O. H., and Loucks, M.: Studies in Intestinal Obstruction: II. The Absorption of Histamine from the Obstructed Bowel, *ibid.* **16**:1089 (May) 1928.

11. Scott, H. G., and Wangenstein, O. H.: Effect of Intravenous Injections of Peritoneal Fluids Recovered from Dogs Dying from Experimental Intestinal Strangulations, *Proc. Soc. Exper. Biol. & Med.* **29**:559, 1932.

peritonitis, many authors¹² have thought that this same or a similar substance produced the toxemia of generalized peritonitis.

Although Steinberg and his co-workers¹³ had previously reported a slight drop in blood pressure occurring during the development of suppurative peritonitis and Whipple¹⁴ had barely mentioned a toxic proteose as being associated with peritonitis, we¹⁵ were the first to demonstrate clearly the action of a vasodepressant toxic substance in peritonitis.

METHOD

It occurred to us that the vasomotor system of another animal might be more sensitive than that of the animal in which peritonitis was present. Normal dogs, weighing from 6 to 14 Kg., whose blood pressures were being observed by the direct method through a carotid cannula, were used as indicators of vasodepressant toxins. In the majority of experiments injections were made intravenously into dogs completely anesthetized with barbital (from 250 to 275 mg. per kilogram of body weight, intraperitoneally or intramuscularly). In some later experiments a few injections were made intraperitoneally into anesthetized dogs and intravenously into unanesthetized dogs. In the latter group, determinations of the blood pressure, when made, were obtained by direct puncture of the femoral artery. In about two thirds of the instances in which a drop in the blood pressure occurred, the same material was also tested by intravenous injection into a rabbit, since it has been shown by Dale and Laidlaw¹⁶ that the vasomotor system of the rabbit responds to histamine with a rise in blood pressure. In every instance in our experiments that a preparation was found to be toxic in the dog, there was a similar action for the rabbit.

The method of Buchbinder, Heilman and Foster¹⁷ of producing suppurative peritonitis by an open isolated intestinal segment, around which the continuity of the intestinal tract was reestablished by end to end or side to side anastomosis, has been used and found reliable. Only two dogs of the fifty so operated on survived. When leakage was present at the site of the anastomosis, the animals were discarded from the series, since Gatch, Trusler and Lyons¹⁸ recently published

12. Orr, T. G., and Hayden, R. L.: Enterostomy in the Treatment of General Peritonitis, *Arch. Surg.* **18**:2159 (April) 1929. Benians, T. H. C.: Further Experiments with Fixation Areas, Bearing on the Pathogenicity of *Bacillus Coli* in Peritoneal Infections, *Brit. J. Exper. Path.* **5**:123, 1924. Bailey, H. A., and Shipley, A. M.: Treatment of Appendicitis Complicated by Peritonitis, *Ann. Surg.* **96**:537, 1932.

13. Steinberg, B.; Kobacker, J. L., and Russel, T. G.: Cardiovascular System in Acute Suppurative Peritonitis, *Proc. Soc. Exper. Biol. & Med.* **30**:1155, 1930.

14. Whipple, G. H.: Proteose Intoxication: Intestinal Obstruction, Peritonitis and Acute Pancreatitis, *J. A. M. A.* **67**:15 (July 1) 1916.

15. Harmon, P. H., and Harkins, H. N.: Depressor Substances in Peritonitis, *Proc. Soc. Exper. Biol. & Med.* **32**:6, 1934.

16. Dale, H. H., and Laidlaw, P. P.: Histamine Shock, *J. Physiol.* **52**:355, 1919.

17. Buchbinder, J. R.; Heilman, F. R., and Foster, G. C.: Experimental Peritonitis: II. The Effect of Hypertonic Dextrose Solution upon Experimental Diffuse Peritonitis, *Surg., Gynec. & Obst.* **49**:788, 1929.

18. Gatch, W. D.; Trusler, H. M., and Lyons, R. E.: Toxemia in Acute Intestinal Obstruction, *Arch. Surg.* **28**:1102 (June) 1934.

results of experiments which showed the direct toxicity of intraperitoneally extravasated pancreaticoduodenal secretion.

Bile peritonitis was produced by three different methods: by the intraperitoneal injection of whole sterile gallbladder bile from dogs, by the intraperitoneal injection of 10 per cent solution of bile salts¹⁹ sterilized either in the autoclave or by filtration through a sterile Berkefeld N filter, and by defundation of the gallbladder after double ligature and division of the common bile duct between ligatures.

Observations on the hemoglobin and the percentage by volume of red cells with a view of determining possible blood concentration were carried out on representative animals in each class of experiments. The Sahli hemoglobinometer (17 Gm. per hundred cubic centimeters equals 100 per cent) and the Van Allen hematocrit were used. The amount of blood obtainable from section of the carotid artery (bleeding volume) was determined on animals from each type of experiment. The latter observations will be presented, with the results of the corresponding experiment, later in the paper.

After a time varying from sixteen to ninety-six hours the peritoneal cavity was reopened under aseptic precautions, the contents were cultured and the peritoneal cavity was aspirated. In those animals in which suppurative peritonitis occurred it was usually necessary to lavage the peritoneum with from 150 to 300 cc. of physiologic solution of sodium chloride in order to obtain most of the purulent material. When bile peritonitis was produced, it was unnecessary to add fluid, since a large quantity of serosanguineous exudate mixed with bile salts or bile was present.²⁰ This exudate is rich in protein and corresponds closely in chemical composition to blood plasma.²¹ The fluid obtained was then centrifugated at high speed for from thirty to forty-five minutes until either a clear or a slightly opalescent supernatant fluid remained. It was then removed carefully from the underlying sediment and from the overlying lipoid film and used in the experiments described here. Intravascular clotting was not observed in any experiments when such fluids were injected intravenously. These experiments were performed over a period of two years but are grouped together for ease in presentation without regard for chronological sequence.

EXPERIMENTAL DATA

EXPERIMENT 1 (table 1).—*Vasodepressant substances associated with peritonitis produced by an open low intestinal loop.*

Peritoneal washings were obtained from fifteen dogs in which suppurative peritonitis had been produced by an open intestinal loop, located within 20 cm. of the ileocecal junction. In many instances, as indicated in the table, opportunity was present for peritoneal lavage on separate days in the same animal. The result

19. Armour's purified bile salts were used.

20. Andrews, E., and Hrdina, L.: The Cause of Death in Liver Autolysis, Surg., Gynec. & Obst. **52**:61, 1931. Andrews, E.; Rewbridge, A. G., and Hrdina, L.: Causation of Bacillus Welchii Infections in Dogs by Injection of Sterile Liver Extracts or Bile Salts, *ibid.* **53**:176, 1931. Mason, E. C., and Lemon, C. W.: Anhydremia as a Possible Cause of Death in Liver Autolysis, *ibid.* **55**:427, 1932. Trusler, H. M., and Reeves, J. R.: Significance of Anaerobic Organisms in Peritonitis Due to Liver Autolysis, Arch. Surg. **28**:479 (March) 1934.

21. Harkins, H. N.; Harmon, P. H.; Hudson, J., and Andrews, E.: Mechanism of Death in Bile Peritonitis, Proc. Soc. Exper. Biol. & Med. **32**:691, 1935. Harkins, H. N.; Harmon, P. H., and Hudson, J.: Lethal Factors in Bile Peritonitis: I. "Surgical Shock," Arch. Surg. **33**:576 (Oct.) 1936.

of a typical experiment is shown in chart 1. An open intestinal segment 27.5 cm. long was established on dog 215 (weight 9.5 Kg.). A side to side anastomosis was made at a point 3.5 cm. from the ileocecal junction. Seventy-five centimeters of intestine remained from the pylorus to the site of anastomosis. The peritoneal cavity was reopened twenty-four hours and again forty-eight hours after the first operation, aseptic lavage of the peritoneum with physiologic solution of sodium chloride being given on each occasion. A marked fall in blood pressure was obtained in tests of the supernatant fluid on other dogs. In the experiment reproduced in chart 1, 120 cc. of almost clear fluid from the centrifugated peritoneal washings was injected into the right femoral vein of dog 110 (weight 7 Kg.). The blood pressure was recorded by the direct method from the right carotid artery, the animal being under barbital anesthesia. The initial blood pressure was 126 mm. The injection required one and a half minutes. The blood pressure began

TABLE 1.—*Depressor Substances in Peritoneal Washings from Dogs with Experimental Suppurative Peritonitis Produced by an Open Intestinal Loop in the Lower Part of the Ileum*

Dog No.	Days After Operation				Results of Bacterial Culture
	1st Day	2d Day	3d Day	4th Day	
25	Present	Heavy growth of Clostridia and B. coli
112	Present	Same as in dog 25
215	Present	Present	Clostridia, B. coli, Str. viridans and Str. haemolyticus
337	Absent	Present	Same as in dog 215
338	Absent	Present	Present	Same as in dog 215 with staphylococci
339	Present	Clostridia, staphylococci and B. coli
442	Present	Clostridia and B. coli
320	Absent	Clostridia, staphylococci and B. coli
549	Absent	B. coli, gram-positive aerobic bacilli and staphylococci
550	Absent	B. coli and clostridia
617	Present	B. coli, Clostridia and Str. haemolyticus
720	Absent	B. coli, few staphylococci and streptococci (died in 9 days)
846	Absent	Staph. albus and B. coli (mild and localized)
1438	Present	B. coli and Str. haemolyticus
1443	Present	B. coli, Str. haemolyticus, Staph. albus and an unidentified gram-positive bacillus

to fall as the injection was being terminated. Five minutes later the blood pressure was 28 mm. A slow rise then ensued, the level in the three steps in the tracing being 38, 70 and 90 mm.

From table 1 it is seen that a certain time is necessary for enough of the toxic substance to develop in the peritoneal cavity to be demonstrable under the conditions of these experiments. In only one of three dogs examined on the first day after the primary operation could the toxic substance be demonstrated, while in three of six examined forty-eight hours after the first operation and in six of seven examined after seventy-two hours the toxic substance was present.

EXPERIMENT 2 (table 2).—*Midintestinal loops.*

These experiments in which five dogs were used are similar to those described under experiment 1, except that the open loop was removed from the intestinal tract at approximately half the distance from the pylorus to the cecum.

While there were not as many animals in this group as in the preceding one, the data do not indicate any difference in the rate of production of the toxic substances in the two sets of experiments.

EXPERIMENT 3 (table 3).—*High intestinal loops.*

In this group eight dogs were used. Care was taken to select for the highest point of the open loop, a level at least 20 cm. below the pylorus, so that the entrance of the common bile duct and at least one of the pancreatic ducts was above the site of anastomosis. The mesenteric border of the open loop, which frequently contained a portion of the pancreas, was carefully examined for accessory pancreatic ducts. Whenever these were found they were divided between double ligatures of silk. These precautions were purposely not observed in the instances of dogs 547 and 548. In these animals especially high sites for the upper portion of the open loop were selected, i. e., 4 and 7 cm. from the pylorus, so that the open loop would contain the entrance of the common bile duct and at least one of the pancreatic ducts. These two dogs died in sixteen and twenty-two hours, respectively.

The peritoneal washings obtained before death from the latter two animals caused a profound drop in blood pressure and could be considered as confirmatory of the findings of Gatch, Trusler and Lyons¹⁸ and of Dragstedt, Haymond and Ellis,²² who reported that activated pancreatic juice within the peritoneum was toxic. Excluding these two special instances, there remains the fact that the

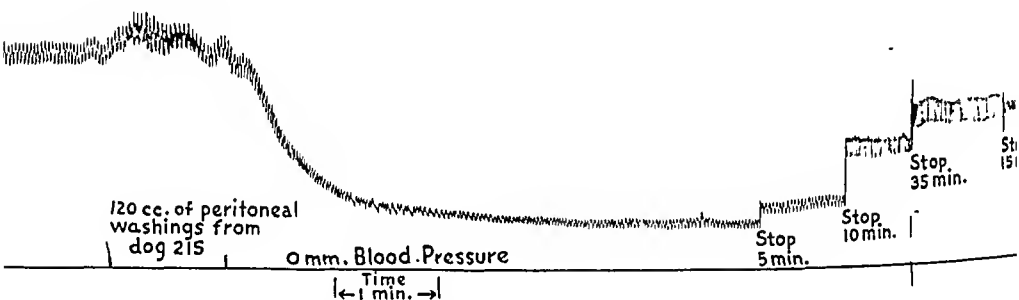


Chart 1.—Blood pressure tracing of a 7 Kg. dog given an intravenous injection of centrifugated peritoneal washings from a dog (no. 215) with suppurative peritonitis. Note the profound and almost immediate drop in arterial blood pressure and the slow return to an almost normal level.

washings from four of six animals were toxic within twenty-four hours after the intestinal loop was opened.

EXPERIMENT 4.—*The exudate in experimental bile peritonitis.*

Nine dogs were used in this division. Bile peritonitis was produced in three groups of three dogs each by the three methods previously indicated. Although the entire supernatant fluid from the centrifugated peritoneal washings of a single dog was injected intravenously into the test animal, no change in blood pressure was noted save the transient pressor effect due to an increase in circulating fluid volume immediately after injection. In a single instance, when the animal was not washed out until an hour after death, a typical profound drop in blood pressure occurred. In six of these instances a large gram-positive obligate anaerobic organism was obtained in pure culture. In two instances the cultures remained sterile.

22. Dragstedt, L. R.; Haymond, H. E., and Ellis, J. C.: Pathogenesis of Acute Pancreatitis, Arch. Surg. 28:232 (Feb.) 1934.

while from the last mentioned animal the gram-positive anaerobic bacillus was obtained in mixed culture with the colon bacillus.

EXPERIMENT 5.—*Control experiment; normal dogs.*

Lavage of the peritoneal cavity of eight normal animals was done. In four instances this procedure was repeated in forty-eight hours. Twelve samples of fluid from normal dogs were thus tested on other dogs. In not a single instance was a fall in blood pressure noted. Cultures for bacteria from these twelve fluids remained sterile.

EXPERIMENT 6.—*Second control experiment; washings after extensive gastrointestinal operations.*

TABLE 2.—*Depressor Substances in Peritoneal Washings from Dogs with Experimental Peritonitis Produced by an Open Loop in the Region of the Scjuno-Ileal Junction*

Dog No.	Days After Operation				Results of Bacterial Culture
	1st Day	2d Day	3d Day	4th Day	
214	Absent	Staph. aureus, B. coli and few Clostridia
230	Absent	Present	.	.	Clostridia and B. coli
770	Present	B. coli and few Clostridia
776	Absent	Present	.	..	B. coli and Clostridia (sterile on 1st day)
840	Present	.	..	B. coli and Clostridia

TABLE 3.—*Depressor Substances in Peritoneal Washings from Dogs with Experimental Peritonitis Produced by an Open Loop in the Duodenum or in the Region of the Duodeno-Jejunal Junction*

Dog No.	Days After Operation				Results of Bacterial Culture
	1st Day	2d Day	3d Day	4th Day	
507	Slight fall	Present	.	.	Clostridia and B. coli
508	Present	.	.	Same as in dog 507
547	Present	Same as in dog 507
548	Present	.	.	.	Same as in dog 507
771	Present	.	.	.	Same as in dog 507
773	Present	.	.	.	B. coli
775	Absent	.	.	.	B. coli and Clostridia
790	Present	.	.	.	B. coli, few Staph. albus and streptococci

In six instances a gastrojejunostomy without excision of any portion of the stomach was done after the method of Eiselsberg for pyloric exclusion, while on two other dogs a similar operation was done by the Billroth II technic. On the fourth postoperative day the peritoneum was reopened, cultures for bacteria were made and the peritoneal contents were removed by the usual method of lavage and aspiration. Table 4 shows the condition of the peritoneum and the results of the cultures for bacteria in these eight dogs. No vasodepressant substance was demonstrated.

EXPERIMENT 7.—*Filtration of toxic peritoneal washings.*

An open loop had been made in the lower level of the ileum of dog 617. On the third day after the primary operation the peritoneal cavity of this dog was reopened, and its content was removed by lavage and aspiration. Cultures of the content yielded *Bacillus coli-communis*, *Streptococcus haemolyticus* and a gram-positive

spore-forming obligate anaerobic organism. The clear supernatant fluid obtained by centrifugation was divided into two portions. One part was passed through a sterile Berkefeld N filter. The filtrate was cultured for bacteria, but no growth was obtained. Portions of both these fluids were then tested by intravenous injection into a normal anesthetized dog (chart 2), with the result that they caused a drop in blood pressure. The first two drops of 50 and 54 mm. were observed with the unfiltered samples, while the latter two drops in the blood pressure of 22 and 26 mm. were observed with the filtered samples. We have observed that succeeding identical doses of this toxic material frequently do not cause as profound a fall in the blood pressure as the initial dose, so that while this experiment possibly indicates some slight loss in potency by filtration, such a conclusion is not certain. The same phenomenon is seen after the intravenous injection of histamine. This experiment was repeated with an identical result with the fluid from dog 508.

EXPERIMENT 8.—*Does atropine abolish the vasodepressant action?*

It has been shown by Dale and Laidlaw¹⁶ and by Simonart²³ that atropine will abolish the fall in the blood pressure that is produced by acetylcholine. Fluids

TABLE 4.—*Appearance of Peritoneum in Dogs Which Had an Extensive Gastro-Intestinal Operation Ninety-Six Hours Previously*

Dog No.	Type of Operation	Appearance of Peritoneum	Results of Culture for Bacteria
152	Elselsberg	20 cc. of free fluid; not hyperemic	B. coli-communis and Staph. albus
153	Elselsberg	Same as in dog 152	B. coli-communis
154	Elselsberg	Same as in dog 152	Staph. aureus
244	Elselsberg	40 cc. of purulent free fluid; moderately hyperemic	Str. haemolyticus, Str. viridans and Clostridia
261	Billroth II	20 cc. of free fluid; not hyperemic	Staph. aureus and an aerobic gram-positive bacillus
333	Billroth II	50 cc. of purulent free fluid; peritoneum markedly hyperemic	B. coli-communis and Clostridia
716	Elselsberg	20 cc. of free fluid; not hyperemic	B. coli-communis, with slight growth of Str. haemolyticus and an aerobic gram-positive bacillus
818	Elselsberg	20 cc. of free fluid; not hyperemic	Staph. aureus and Clostridia

from all eight animals used in this division had been previously shown to lower the blood pressure. Atropine sulfate, 0.8 mg., was then injected intravenously into the test animal in each case. The same dose of fluid that occasioned the first observed drop in the blood pressure was then readministered intravenously.

No single response was obtained in all dogs (charts 3 and 4). Atropine sulfate partially abolished the drop in blood pressure caused by the fluid from dog 339, while it had no effect on the reaction produced by the fluid from dog 338. Atropine sulfate rendered the test animals given the fluid from dogs 337 and 442 totally refractory to a second dose of the fluid. The fluid from dog 617 was similar to that from dog 339, as atropine sulfate partially abolished its depressant effect. Since there was an indication that a second dose of a vasodepressant fluid did not produce the same drop in blood pressure as the first, a few tests were made only after atropinization of the test animal. The results of such tests were com-

23. Simonart, A.: On the Action of Certain Derivatives of Choline, J. Pharmacol. & Exper. Therap. 46:157, 1932.

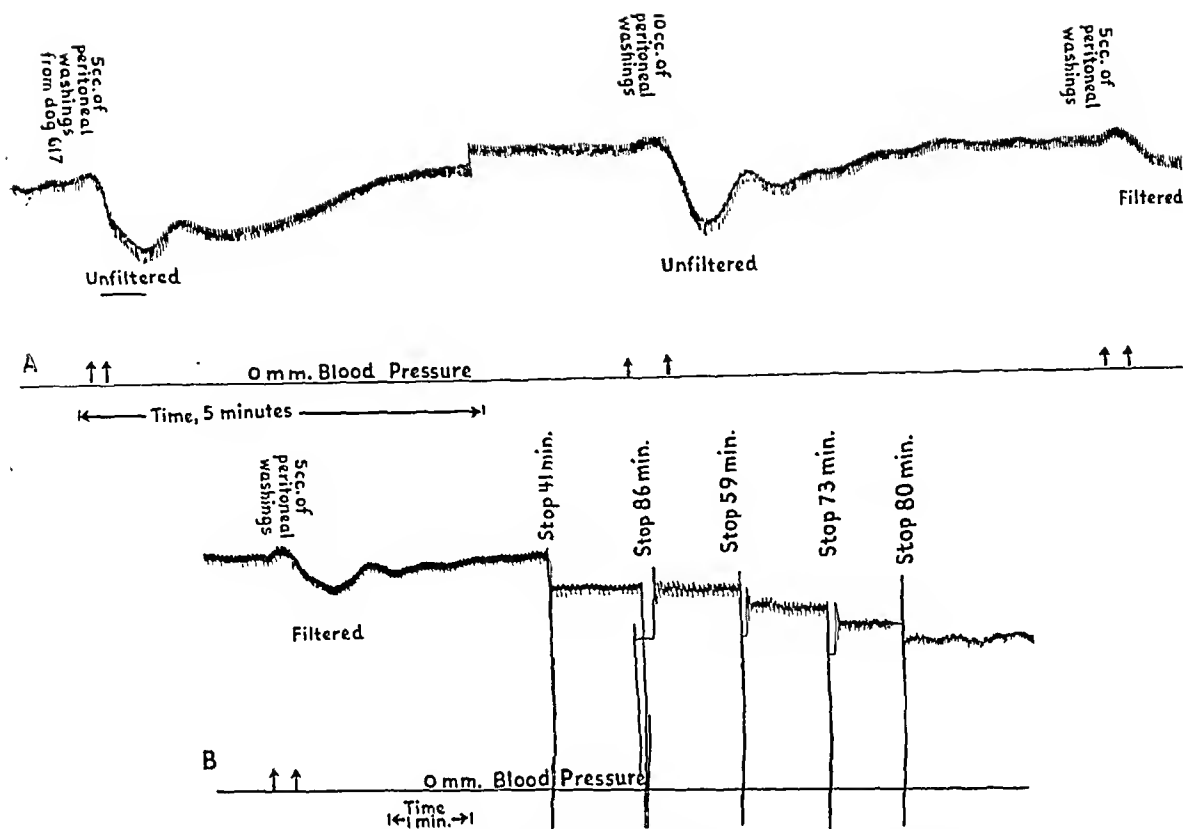


Chart 2.—The comparative effect on the blood pressure of centrifugated peritoneal washings from dog 617 from an open intestinal loop seventy-two hours after operation before and after passage through a Mandler filter. Blood pressure observations were made over six and one-half hours.

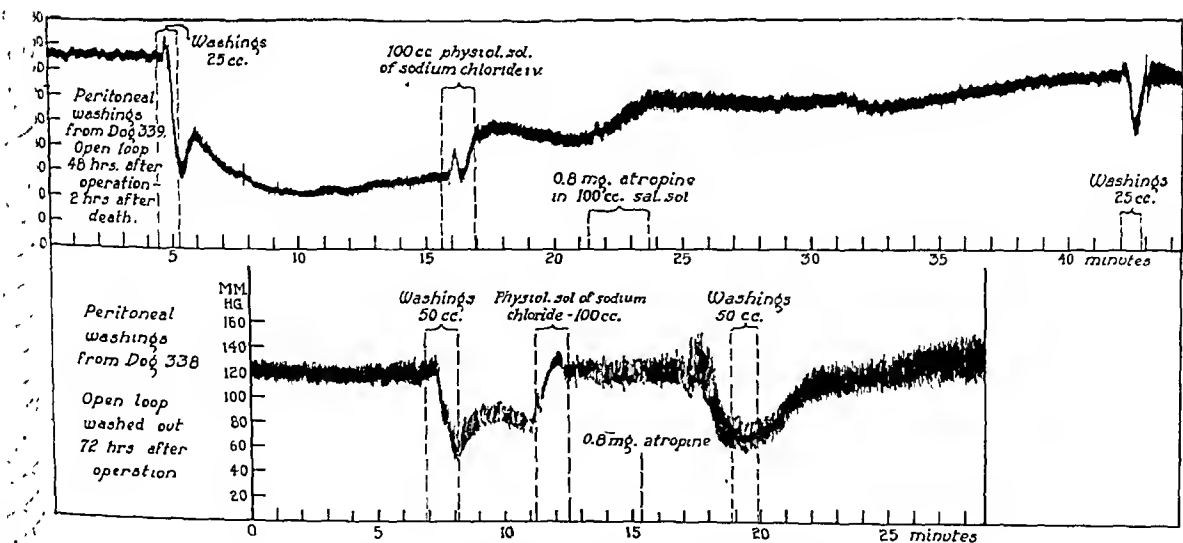


Chart 3.—Comparison of vasodepressant action of centrifugated peritoneal washings before and after the administration of atropine. Blood pressure tracings from two dogs (338 and 339) each given an injection of peritoneal washings from a separate dog. Note variations in the drop in the blood pressures with the same test dose.

pared with the drop in blood pressure in other unatropinized animals (chart 4). In this particular experiment (peritoneal washings from dog 840) it can be seen that atropine sulfate completely abolished the reactivity of the vasodepressant system to the depressant substance, regardless of whether it was given initially or after vasodepressant doses of the peritoneal washings.

EXPERIMENT 9.—Symptoms produced by active fluids.

(a) A vasodepressant fluid, of which 5 cc. caused a fall in blood pressure of 58 mm., was obtained from dog 617. This fluid was then injected intravenously without anesthesia into dogs 817 and 818 in quantities of 18 and 30 cc., respectively. Dog 817 had an emesis of about 150 Gm. of partially digested stomach contents ten minutes after injection and then appeared disinclined to walk around the room. Dog 818 seemed not to have been affected by the injection. Four hours after the

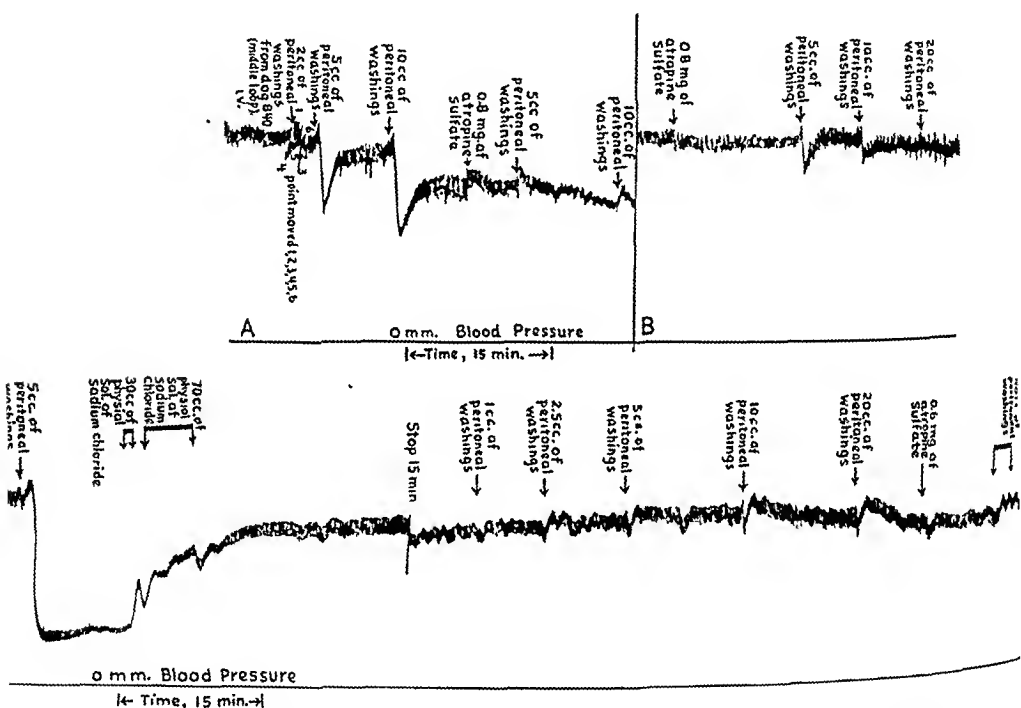


Chart 4.—Relation of varied time of atropinization to the effect on the blood pressure of active peritoneal washings. In *A* and *B* atropine sulfate practically abolished all reactivity of the vasodepressant substance, while in *C* the effect of atropine sulfate is uncertain because repeated injections of peritoneal fluid were without effect even prior to the administration of atropine.

injection both dogs appeared as before the material was administered and remained well over a four week period of observation.

(b) A similar vasodepressant fluid, of which 10 cc. caused a fall of 80 mm. in blood pressure, was obtained from dog 443. This fluid was then injected intravenously without anesthesia into three dogs in quantities of 10, 20 and 60 cc., respectively. The first two dogs appeared only unwilling to walk about the room, but the one receiving 60 cc. of the fluid had a large watery emesis twenty minutes after injection. Recurrence of emesis was noted frequently during the ensuing

ten hours. Sixteen hours after injection all three dogs appeared to be normal and were still well four weeks later.

EXPERIMENT 10.—*Blood pressure drop in unanesthetized animals.*

Twenty-three cubic centimeters of a peritoneal washing from dog 771, which in a previous experiment had caused a drop of 84 mm., was given intravenously to a normal unanesthetized dog. The blood pressure was recorded by puncture of the femoral artery. Prior to injection the blood pressure was 134 mm.; three minutes after injection it fell to 56 mm. The animal struggled for a few minutes and then became weak, but soon improved and was able to stand in twenty minutes. A loose stool was passed in the interim. A similar experience occurred with two other unanesthetized dogs treated in this way.

EXPERIMENT 11.—*Intraperitoneal injection of vasodepressant fluids.*

Toxic peritoneal washings were injected intraperitoneally into each of five dogs. Four were anesthetized with barbital and one with morphine and ether. Tracings from two of these animals are reproduced in chart 5, while chart 6 shows a record of the blood pressure of the animal anesthetized by morphine and ether.

TABLE 5.—*Hemoglobin Content and Hematocrit Readings on Dogs During the Development of Peritonitis*

Dog No.	Distance from Pylorus to Open Segment, Cm.	Interval (Hr.) Between		Hemoglobin Percentage (Sahli)		Hematocrit Reading (%)		Toxicity of Peritoneal Washings
		Operation and Lavage	Lavage and Death	Before Operation	After Peritonitis	Before Operation	After Peritonitis	
770	108	20	11	116	140	53	58	+
771	4	27	0.25	96	128	42	50	+
775	6	17	3	102	106	47	52	0
776	128	26	18	118	130	50	54	+

From 5 to 15 cc. of the peritoneal washings obtained from dog 845 produced a drop of 34 and 36 mm., respectively, on intravenous administration. But a drop of only 20 mm. in one hundred and twenty-six minutes resulted from intraperitoneal injection of 40 cc. of the same fluid. The active peritoneal washing from dog 840 caused a drop of 8 mm. in sixty-six minutes. In another experiment 50 cc. of a peritoneal washing, of which 5 cc. caused a drop in blood pressure of 42 mm. on intravenous injection, caused a decline in blood pressure from 146 to 106 mm. in twenty-four minutes after intraperitoneal injection. Since there is a slight drop in blood pressure over such periods of time in certain barbitalized animals, another experiment (chart 6) was performed, morphine and ether anesthesia being used. Reference to this figure shows the unmistakable action of the vasodepressant substance after intraperitoneal administration.

EXPERIMENT 12.—*Fluid loss from the blood during development of experimental suppurative peritonitis.*

In four animals observations were made on the hemoglobin content and the percentage by volume of red blood cells during the development of peritonitis. These values are seen in table 5. Observations were not made on the blood pressure of these animals.

It is seen that during the development of peritonitis in these animals there is some slight concentration in blood, as evidenced by a slight rise in hemoglobin and hematocrit values. This change was not marked and can be easily accounted

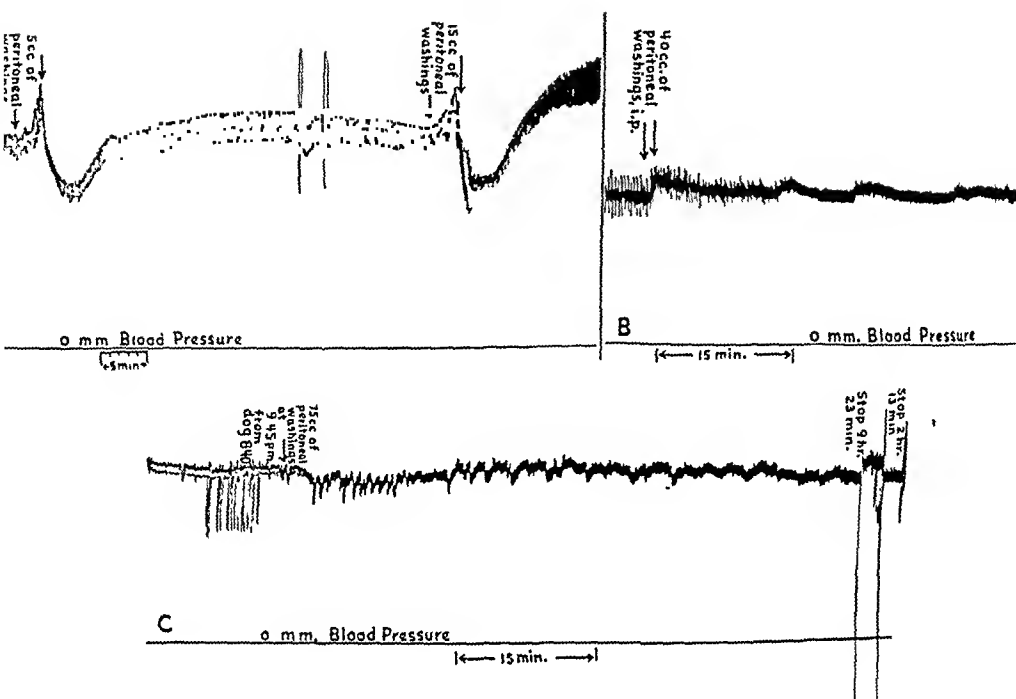


Chart 5.—Comparison of the vasodepressant effect of active peritoneal washings administered by various routes: *A*, intravenously; *B*, intraperitoneally and *C*, intraperitoneally. Although not reproduced in these tracings, the peritoneal washings from dog 840 were a potent preparation. Note the primary pressor effect with the washings from dog 845 in *B*.

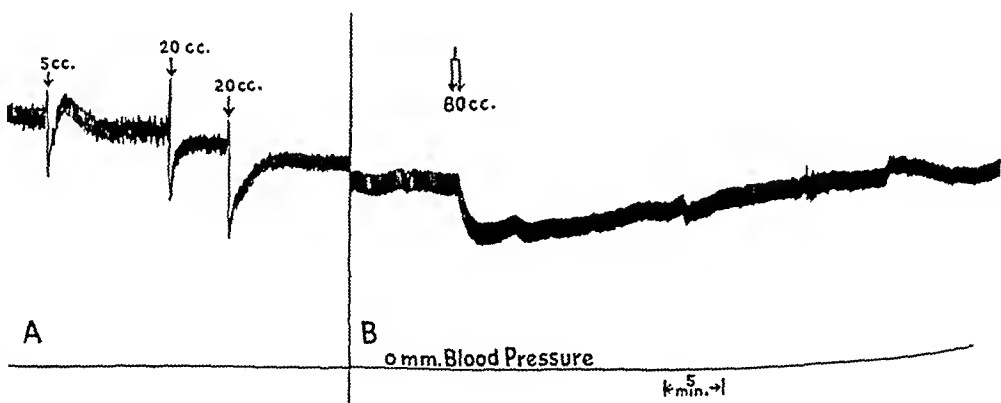


Chart 6.—Comparison of vasodepressant effects of active peritoneal washings given in varying doses (*A*) intravenously and (*B*) intraperitoneally. Note the sustained fall in blood pressure when the material was given by the latter route. (The test animal used for the intraperitoneal injection was given morphine-ether anesthesia.)

for by the emesis that occurred and by the fact that fluids were withheld. No significant amounts of fluid were seen within the abdominal cavities of these animals when they were opened for peritoneal lavage.

EXPERIMENT 13.—*Shock syndrome produced by active peritoneal fluids.*

Observations were also made on the blood pressure, the hemoglobin content, the percentage (by volume) of red cells and the bleeding volume in seven dogs that had received repeated intravenous injections of toxic peritoneal fluid sufficient to lower the blood pressure to a shock level. A record of these findings is given in table 6. It is seen that there was no significant change in the hemoglobin and hematocrit readings. The average bleeding volume obtained in terms of percentage of the calculated blood volume was 54.3. Such observations place the action of this substance in the category of primary shock analogous to the type induced by the administration of histamine.²⁴

TABLE 6.—*Data on Blood Pressure, Bleeding Volume, Percentage (by Volume) of Red Cells and Hemoglobin Content of Dogs Receiving Active Peritoneal Washings Intravenously*

Dog No.	Weight. Kg.	Blood Pressure		Time (Min.) Between Initial Observation and Bleeding at Shock		Hemoglobin Percentage		Hematoerit Reading		Bleeding Volume	
		Initial	Prior to Bleeding	at Point of Low Blood Pressure	Time (Min.) Blood Remained Below 80 Min. Pressure	Initial	Prior to Bleeding	Initial	Prior to Bleeding	Cc.	Percentage of Calculated Blood Volume
767	5.5	122	68	12	5.5	104	106	43	43	228	53.9
813	6.5	126	62	29	16	78	92	35	38	270	54.0
816	6.0	134	46	21	10	82	106	41	46	265	57.5
817	7.5	154	34	37	20	118	120	51	50	210	37.7
818	5.0	138	80	32	13	108	98	43	44	215	55.9
819	7.0	130	72	59	9	92	92	42	40	247	46.1
820	6.0	126	26	14	5	80	82	40	..	255	55.3
Average bleeding volume (percentage of calculated blood volume), all experiments...										54.3	

COMMENT AND SUMMARY

These experiments demonstrate the presence of a vasodepressant toxin occurring in the peritoneal cavity coincident with the development of suppurative peritonitis. The earlier experiments in this series (tables 1, 2 and 3) demonstrate clearly that a definite time is required for the development of this toxic product. The toxin or toxins seem to appear earlier when the open intestinal segment is placed high in the gastro-intestinal tract, where opportunity is greatest for soiling the upper portion of the abdomen. The nature of the experiments was such as to rule out effectively the possibility of inherent toxicity of the

24. Roome, N. W.; Keith, W. S., and Phemister, D. B.: Experimental Shock; The Effect of Bleeding After Reduction of the Blood Pressure by Various Methods, Surg., Gynec. & Obst. 56:161, 1933.

pancreaticoduodenal secretion, a factor that has been recently demonstrated by Gatch and his co-workers.¹⁸

The identity of this toxic substance has not been fully elucidated in this series of experiments. It is highly probable in view of the variable response obtained on the blood pressure after atropinization that there is more than one substance involved. Either acetylcholine or a like substance is definitely present in certain of these preparations. Demonstration that these fluids lower the blood pressure in rabbits as well as in dogs is definite evidence that histamine is not the major substance involved. That some or all of these vasodepressant substances are filtrable through a bacteria-tight filter, that they are active on absorption from the peritoneum and that they lower blood pressure and produce symptoms of weakness and hypermotility of the gastro-intestinal tract in normal unanesthetized dogs is also demonstrated in these experiments.

It is well known that toxic amines can be obtained by extraction in saline solution from practically all the body tissues, including the peritoneum, after death. Our experiments were performed so as to obtain peritoneal washings many hours and at times even days prior to death from suppurative peritonitis. Thus, the question of agonal invasion has been avoided. It is noteworthy that cultures for bacteria gave a rich flora from the peritoneum in all our animals. The colon bacillus and a gram-positive spore-forming obligate anaerobic organism resembling the Welch bacillus were invariably reclaimed, and usually staphylococci and streptococci. The question would naturally arise as to whether these micro-organisms produced a vasodepressant toxin in their growth within the peritoneum. This is being investigated further. That the colon bacillus or its growth products may be the most important source of this toxic substance is suggested by the fact that the fluid from experimentally induced bile peritonitis is devoid of a vasodepressant substance even when the entire peritoneal exudate is injected intravenously into a test animal at the stage when gram-positive obligate anaerobic organisms can be easily cultured. However, if death occurs and the peritoneal fluid is removed even as soon as a half-hour after death, there is a vasodepressant toxin present. At this time the colon bacillus as well as the anaerobe can be cultured. The identification and significance of the anaerobe in bile peritonitis will be discussed elsewhere.²⁵ Further studies are also being made on the chemical nature of this vasodepressant substance.

The similarity of the action of this depressant substance and that obtainable from normal fecal material and from the contents of

25. Harmon, P. H., and Harkins, H. N.: Peritonitis: II. The Effect on Blood Pressure of Protein-Free Extracts of the Peritoneal Content and of Filtrates from Pure Cultures of Bacteria, *Arch. Surg.*, this issue, p. 580.

obstructed bowel is striking. A comparison of our blood pressure tracings with those demonstrated by Gatch and his co-workers,¹⁸ who dealt with the latter materials, reveals this marked similarity.

Our experiments do not elucidate the exact rôle that these toxic substances play in the fatal decline from suppurative peritonitis. It is generally believed that absorption is slowed from an inflamed peritoneum, especially if there is a fibrinous exudate present. With such a substance present within the peritoneum in large quantities, it is highly possible that some absorption can and does take place. So far as we can determine from the literature, this is the first adequate demonstration of the association of such a substance with peritonitis, although some relatively insignificant falls in blood pressure in animals in which the condition developed were reported by Steinberg and his co-workers¹³ and a "toxic proteose" was mentioned by Whipple.¹⁴

CONCLUSIONS

A vasodepressant toxic substance in the exudate of experimental suppurative peritonitis is demonstrated, and the conditions for its presence are outlined.

No similar substance was demonstrated in the exudate of bile peritonitis prior to death, or in the normal peritoneum or the soiled peritoneum without diffuse suppurative inflammation.

These toxic fluids were still active after filtration through a bacteria-tight filter. Because of their action after atropinization of the test animal, it is probable that acetylcholine or a similar substance is present in some instances. Histamine is not a significant component of these fluids.

The picture of shock produced by these toxic peritoneal fluids is a primary type of shock, since the blood pressure may be low while the bleeding volume approximates that of normal animals.

PERITONITIS

II. THE EFFECT ON BLOOD PRESSURE OF PROTEIN-FREE EXTRACTS OF THE PERITONEAL CONTENT AND OF FILTRATES FROM PURE CULTURES OF BACTERIA

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In previous experimental studies on peritonitis, we demonstrated¹ a vasodepressant toxic substance in peritoneal washings. The washings from normal animals and from animals on which an extensive gastrointestinal operation had been done, as well as washings from animals with experimental bile peritonitis, were innocuous under the same experimental conditions. Since the vasodepressant toxin occurred in the exudate after death from bile peritonitis, we suspected that the colon bacillus or one of the large gram-positive obligate anaerobic organisms might be a possible source of the substance. This association of bacteria with the production of a toxic substance has been demonstrated by many authors² in experimental intestinal obstruction and in experi-

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From the Douglas Smith Foundation and from the Service of Dr. Edmund Andrews, Department of Surgery, the University of Chicago.

1. Harmon, P. H., and Harkins, H. N.: Studies in Peritonitis: I. The Effect on Blood Pressure of the Peritoneal Content in Suppurative and in Bile Peritonitis, *Arch. Surg.*, this issue, p. 565.

2. Murphy, F. T., and Brooks, B.: Intestinal Obstruction: An Experimental Study of the Cause of Symptoms and Death, *Arch. Int. Med.* **15**:392 (March) 1915. Whipple, G. H.; Stone, H. B., and Bernheim, B. M.: Intestinal Obstruction, *J. Exper. Med.* **17**:286 and 307, 1913. Dragstedt, L. R.; Moorehead, J. J., and Burcky, F. W.: The Nature of the Toxemia of Intestinal Obstruction, *Proc. Soc. Exper. Biol. & Med.* **14**:17, 1916; Intestinal Obstruction: An Experimental Study of the Intoxication in Closed Intestinal Loops, *J. Exper. Med.* **25**:421, 1917. Dragstedt, L. R.; Dragstedt, C. A.; McClintock, J. T., and Chase, C. S.: Intestinal Obstruction: II. A Study of the Factors Involved in the Production and Absorption of Toxic Materials from the Intestine, *ibid.* **30**:109, 1919. Gerard, R. W.: The Lethal Agent in Acute Intestinal Obstruction, *J. A. M. A.* **79**:1581 (Nov. 4) 1922; Chemical Studies on Intestinal Intoxication, *J. Biol. Chem.* **52**:111, 1922. Foster, W. C., and Hausler, R. W.: Acute Intestinal Obstruction: III. Simple Obstruction, *Arch. Int. Med.* **36**:31 (July) 1925. Wangensteen, O. H., and Chunn, S. S.: Studies in Intestinal Obstruction: I. A Comparison of the Toxicity of Normal and Obstructed Intestinal Content, *Arch. Surg.* **16**:606 (Feb.) 1928. Wangensteen,

mental acute pancreatic necrosis. It has likewise been known for a long time that the colon bacillus³ and allied organisms⁴ produce a toxic substance that brings about rapid death when administered to laboratory animals by the intravenous or the intraperitoneal route. When given by the oral route these substances are inactive,⁵ except when obtained by special technical methods.⁶ It remained for Steinberg and Ecker⁷ to show that the lethal agent of the colon bacillus could be specifically neutralized by an antiserum. None of these investigators have pointed out the mechanism by which death occurs when these substances are given. Symptoms are produced by the intravenous injection of the alleged toxin of intestinal obstruction and the toxin of acute pancreatic necrosis that are similar to those obtained by the parasympathetic stimulants of the choline group.⁸

In a review of the bacteriologic literature, it was found that broth cultures of the Welch bacillus⁹ and allied organisms¹⁰ possessed a vaso-

O. H., and Loucks, M.: Studies in Intestinal Obstruction: II. The Absorption of Histamine from the Obstructed Bowel, *ibid.* **16**:1089 (May) 1928. Scott, H. G., and Wangenstein, O. H.: Effect of Intravenous Injections of Peritoneal Fluids Recovered from Dogs Dying from Experimental Strangulations, *Proc. Soc. Exper. Biol. & Med.* **29**:559, 1932. Dragstedt, L. R.; Haymond, H. E., and Ellis, J. C.: Pathogenesis of Acute Pancreatitis, *Arch. Surg.* **28**:232 (Feb.) 1934.

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9. Kojima, K.: Ueber dem Chemismus der Toxinbildung durch den Bacterium phlegmonis emphysematosae, Frankel., *Biochem. Ztschr.* **128**:519, 1923.

10. Kojima, K.: Beitrage zur Erforschung der Rauschbänderreger, *Ztschr. f. Immunitätsforsch. u. exper. Therap.* **37**:170, 185 and 203, 1923. Kendall, A. I., and Schmitt, F. O.: Studies in Bacterial Metabolism: LXXXI. Physiological Action of Certain Cultures of the Gas Bacillus, *J. Infect. Dis.* **39**:250, 1926.

depressant effect. Such facts are not as yet established in investigations of toxic cultures of the colon bacillus unless one excepts the recent experiments of Imanaga,¹¹ who showed that cultures of colon bacilli produce intestinal paralysis. This author did not investigate the effect of his cultures on the blood pressure. In a further study of the vaso-depressant substances associated with bacterial peritonitis, we have investigated their relation to the choline group of vasodepressants and the effect on the blood pressure of toxic filtrates from certain of the bacteria generally associated with suppurative peritonitis. Preliminary communications of the results of these investigations have already appeared.¹² A detailed account follows.

EXPERIMENTS

The method of Chang and Gaddum¹³ was used in preparing protein-free extracts of various materials: the peritoneal washings from animals with suppurative peritonitis, the peritoneal exudate from animals with experimental bile peritonitis, autoclaved 10 per cent solutions of bile salts,¹⁴ the centrifugated sediments obtained in clearing the first two mentioned materials by centrifugation for intravenous injection, the supernatant fluid obtained in the same way and the sediments obtained in centrifugating whole broth cultures of colon bacilli, streptococci and staphylococci prior to preparation of a Berkefeld filtrate from them. This method consists in adding an equal volume of 10 per cent trichloroacetic acid to the fluid to be tested, or from 2 to 5 cc. of the acid to each estimated gram of solid material to be extracted. The mixture is allowed to stand with occasional stirring for from one to two hours and is then filtered through a Buchner funnel. The filter paper on the funnel is washed with from 5 to 20 cc. of 10 per cent trichloroacetic acid. The filtrate is then shaken with ether four or five times in a separatory funnel, the ethereal layer being discarded. The water-clear lower layer is then concentrated by *in vacuo* distillation at from 37 to 40 C. to a 10 to 15 cc. volume (representing generally a fivefold to tenfold concentration by this method). The solution is then titrated to neutrality to congo red with tenth-normal sodium hydroxide. Precautions were taken in the instances of the fresh peritoneal washings and exudates to mix the fluid with trichloroacetic acid immediately on removal from the animal's body to avoid possible disintegration or destruction of any vaso-depressant substance.

These extracts were tested for their effect on blood pressure both in dogs and in rabbits, in comparison with the action of known amounts of acetylcholine solution. In all, forty-one extracts were prepared, and each was tested for its

11. Imanaga, H.: *Experimentelle Untersuchungen über den Entstehungsmechanismus der Darmlähmung bei akuter diffuser Peritonitis*, Deutsche Ztschr. f. Chir. **244**:156, 1934.

12. Harmon, P. H., and Harkins, H. N.: *Depressor Substances in Peritonitis*, Proc. Soc. Exper. Biol. & Med. **32**:6, 1934; *Bleeding Volume in Experimental Colon Bacillus Intoxication*, *ibid.* **32**:1144, 1935.

13. Chang, H. C., and Gaddum, J. H.: *Choline Esters in Tissue Extracts*, J. Physiol. **79**:255, 1933.

14. Armour's purified bile salts were used.

effect on at least two animals of each mentioned species both before and after atropinization. The sensitivity of each test animal was determined by a series of injections of acetylcholine, usually from 1 to 5 micrograms.¹⁵ Although this was not pointed out by Chang and Gaddum, blank extracts prepared by substituting distilled water for the substance to be extracted gave a minor drop of blood pressure in rabbits of from 4 to 5 mm., the equivalent of 0.05 microgram of acetylcholine. There was no difficulty, however, in selecting the extracts that gave a vasodepressant action, since the reactions were of the magnitude of from 1 to 5 micrograms per cubic centimeter, as expressed in terms of acetylcholine equivalents.

The vasodepressant action of these extracts paralleled the activity of the original materials tested; that is, whenever the vasodepressant toxin was present in the original material, the corresponding extract also contained a vasodepressant substance. About a third decrease in activity was noted after atropinization, thus showing the presence of acetylcholine. Extracts prepared from centrifugated sediments from both bacterial peritonitis and from bile peritonitis contained especially large quantities of vasodepressant substance, averaging from 1 to 2 acetylcholine equivalents per cubic centimeter. Here, again, the activity was only partially abolished after atropinization. The extracts from centrifugated fluids from all the instances of bile peritonitis were innocuous, similar to the effect of the original material. The original partially purified bile salt solution used in these experiments yielded a potent vasodepressant substance on extraction. None of the extracts prepared from bacterial sediments had a vasodepressant effect in these tests. The blood pressure of the rabbit was found to be a more sensitive indicator of small amounts of vasodepressant substance than that of the dog.

Since our earlier experiments pointed to the probable close relationship of the colon bacillus in the production of the vasodepressant substance, we have carried out tests on the effect of bacteria-free filtrates from broth cultures of this organism. We have extended these observations to other aerobic organisms, such as streptococci and staphylococci, as well as certain of the gram-positive spore-forming anaerobes, all frequently cultured from the peritoneal content in suppurative peritonitis. The actual source of these organisms varied: Of eleven strains of colon bacilli, eight were from urine obtained at cystoscopy and one was from pus obtained in a case of clinical peritonitis, one from the wall of the gallbladder in a case of chronic cholecystitis and one from a subcutaneous infection of the wound; of two strains of *Streptococcus haemolyticus*, one was obtained in a case of streptococcic peritonitis and another in a case of acute mastoiditis; one strain of *Streptococcus viridans* was isolated from urine; two strains of *Staphylococcus aureus* were isolated from subcutaneous abscesses. The identity of these strains of colon bacilli was verified by carbohydrate fermentations. Two strains of *Clostridium Welchii* and a strain each of *Clostridium sporogenes*, *Clostridium Chauvei* and *Vibrio septicus* had been carried as identified stock cultures in the laboratory for several years.

In the case of the aerobic organisms, 200 cc. of peptone-free veal infusion broth was inoculated with 2 cc. of a heavy twenty-four hour broth culture of the organism and set aside in the incubator for from four to twenty days. Anaerobic cultures were made by the usual technic in deep tubes containing dried beef heart overlaid with 20 cc. of the same peptone-free veal infusion broth. These cultures were sealed with petrolatum. At the end of the incubation periods these small quantities of culture were pooled for each organism, centrifugated for one hour at high speed and then passed through a sterile Berkefeld N filter. Filtration was repeated in the instance of the aerobic organisms in order to insure a bacteria-free

15. A microgram is 0.001 mg., or 0.000001 Gm.

filtrate. Cultures of these filtrates remained sterile. Portions of them were then tested on the blood pressure of dogs under anesthesia induced by either barbital, from 250 to 275 mg. per kilogram, or ethyl carbamate (urethane), 1.5 Gm. per kilogram. Observations were made on the blood pressure of control dogs by the intravenous injection of peptone-free veal infusion broth.

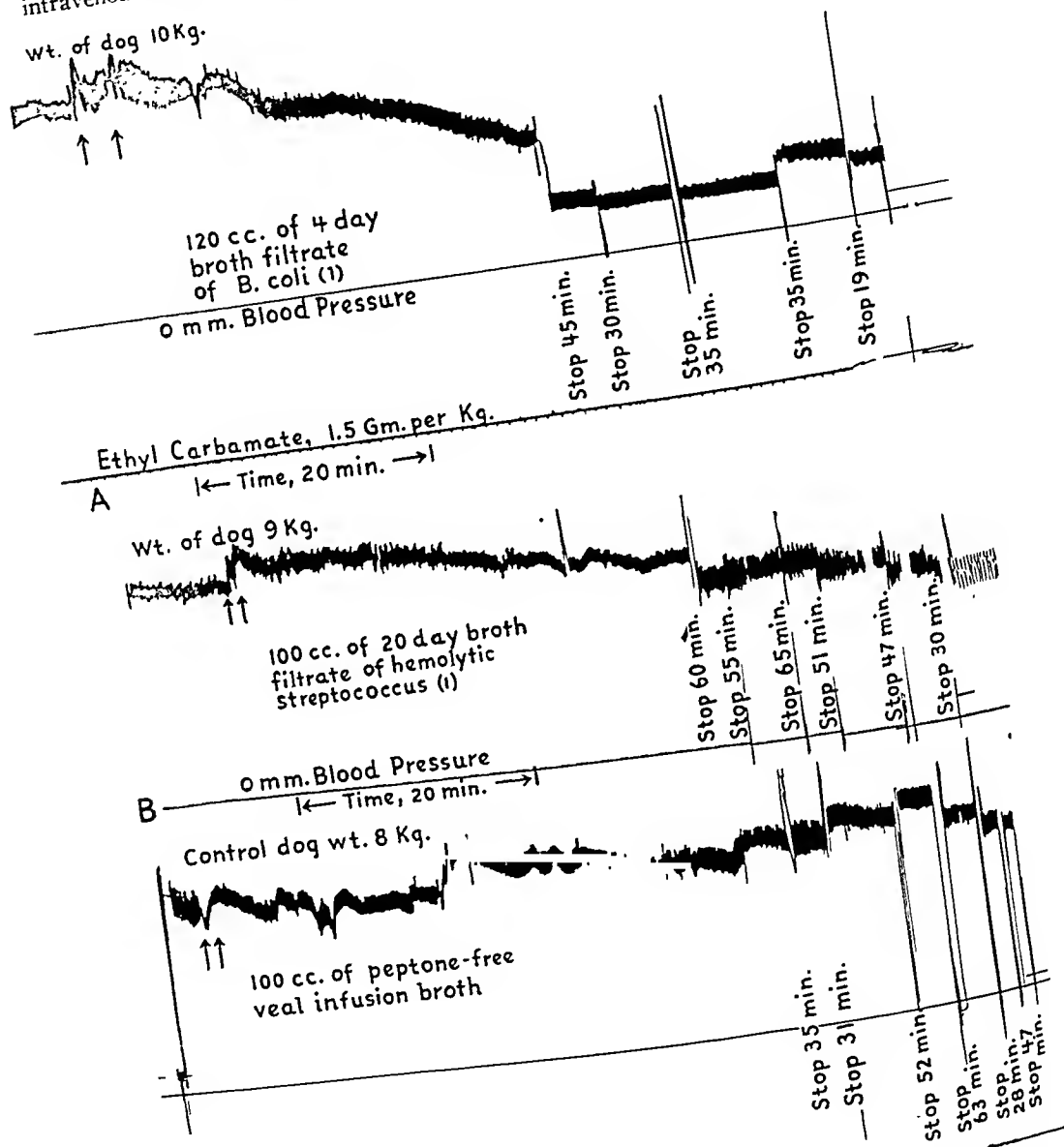


Chart 1.—Comparison of the effects of bacteria-free filtrates from aerobic organisms on blood pressure. *A* shows the effect of a filtrate of a four day culture of colon bacilli; *B*, the effect of a filtrate of hemolytic streptococcus and *C*, the effect of peptone-free veal infusion broth administered intravenously to a control dog. Note the marked vasodepressant effect of colon bacillus filtrate in *A*.

When filtrates of the colon bacillus were given intravenously (charts 1 and 2 and table 1), there was a slow decline in the blood pressure to a shock level, from thirty minutes to two or three hours being required for the minimal level to

TABLE 1.—*Effect of Sterile Filtrates from Certain Aerobic Bacteria on Blood Pressure in the Dog*

Organism and Source	Age of Culture, Days Prior to Filtration	Quantity Used for Test, Cc.	Effect on Blood Pressure; Drop (Mm. of Hg) from Average Initial to Average Final Reading
B. coli-1 (dog with peritonitis).....	4	100	Profound delayed drop
B. coli-1 (dog with peritonitis).....	8	50	Profound delayed drop
B. coli-1 (dog with peritonitis).....	20	100	B. P. 100-90 in 2 hr.
B. coli-2 (cystoscopic urine).....	4	90	B. P. 168-70 in 1½ hr.
B. coli-2 (cystoscopic urine).....	20	90	B. P. 126-70 in 20 min.
B. coli-3 (chronic cholecystitis).....	7	35	B. P. 158-32 in 1½ hr.
B. coli-4 (cystoscopic urine).....	7	100	B. P. 154-46 in 1½ hr.
B. coli-5 (cystoscopic urine).....	7	50	B. P. 126-42 in 2 hr. with death
B. coli-6 (cystoscopic urine).....	7	40	B. P. 146-58 in 3 hr. with death
B. coli-7 (cystoscopic urine).....	7	50	B. P. 164-40 in 5¼ hr.
		43	B. P. 132-52 in 1½ hr.
B. coli-8 (cystoscopic urine).....	7	50	B. P. 166-42 in 2 hr.
		33	B. P. 162-82 in 2¼ hr.
B. coli-9 (wound infection).....	7	50	B. P. 124-86 in 2¼ hr.
		40	B. P. 148-54 in 2 hr.
B. coli-10 (cystoscopic urine).....	7	40	B. P. 164-66 in 2 hr.
B. coli-11 (cystoscopic urine).....	7	50	B. P. 134-38 in 5½ hr.
Str. haemolyticus-1 (streptococcal peritonitis)	2	120	Immediate drop in blood pressure of 40 mm. (no delayed drop)
Str. haemolyticus-1 (streptococcal peritonitis)	4	140	B. P. 112-80 in 6 hr.
Str. haemolyticus-1 (streptococcal peritonitis)	8	80	40 mm. (no delayed drop)
			B. P. 160-140 in 4 hr.
Str. haemolyticus-2	4	100	B. P. 140-120 in 6 hr.
	20	75	Profound immediate drop with rapid recovery; no late drop
Str. viridans (cystoscopic urine)....	4	100	B. P. 102-110 in 7 hr.
Str. viridans (cystoscopic urine)....	20	90	B. P. 152-134 in 3 hr.
Staph. aureus-1 (abscess).....	4	100	B. P. 118-114 in 8 hr.
Staph. aureus-1 (abscess).....	20	55	Profound immediate drop with rapid recovery; no late drop
Staph. aureus-2 (abscess).....	4	100	B. P. 100-72 in 6 hr.
Staph. aureus-2 (abscess).....	20	100	B. P. 108-90 in 5 hr.
Uninoculated peptone-free veal infusion broth (control)	..	100	No change in blood pressure
	..	100	B. P. 124-114 in 6 hr.
	..	120	B. P. 116-90 in 9 hr.
	..	130	B. P. 113-110 in 3 hr.
	..	200	B. P. 146-130 in 3 hr.
	..	200	B. P. 110-90 in 5 hr.

be reached. In most instances death occurred after several hours with a depressed blood pressure. An illustrative experiment is reproduced in tracing A of chart 1. In this instance a 10 Kg. dog was given an intravenous injection of 120 cc. of a

filtrate from a four day culture of colon bacilli. The initial blood pressure of 122 mm. gradually declined to 34 mm. in one hundred minutes. The animal died three hours and forty minutes later. There was no case of an immediate drop in the blood pressure in tests of these filtrates of colon bacilli (eleven strains tested in seventeen dogs), but in every instance there was a profound delayed drop in the blood pressure to a shock level (table 1). The results of the intravenous injection of filtrates of colon bacilli into two other dogs are shown in chart 2.

DOG 1, wt 12.5 Kg
260 mg of barbital
per Kg 9 a.m.

40 cc. of 7 day
filtrate of B.coli
11:15 a.m.

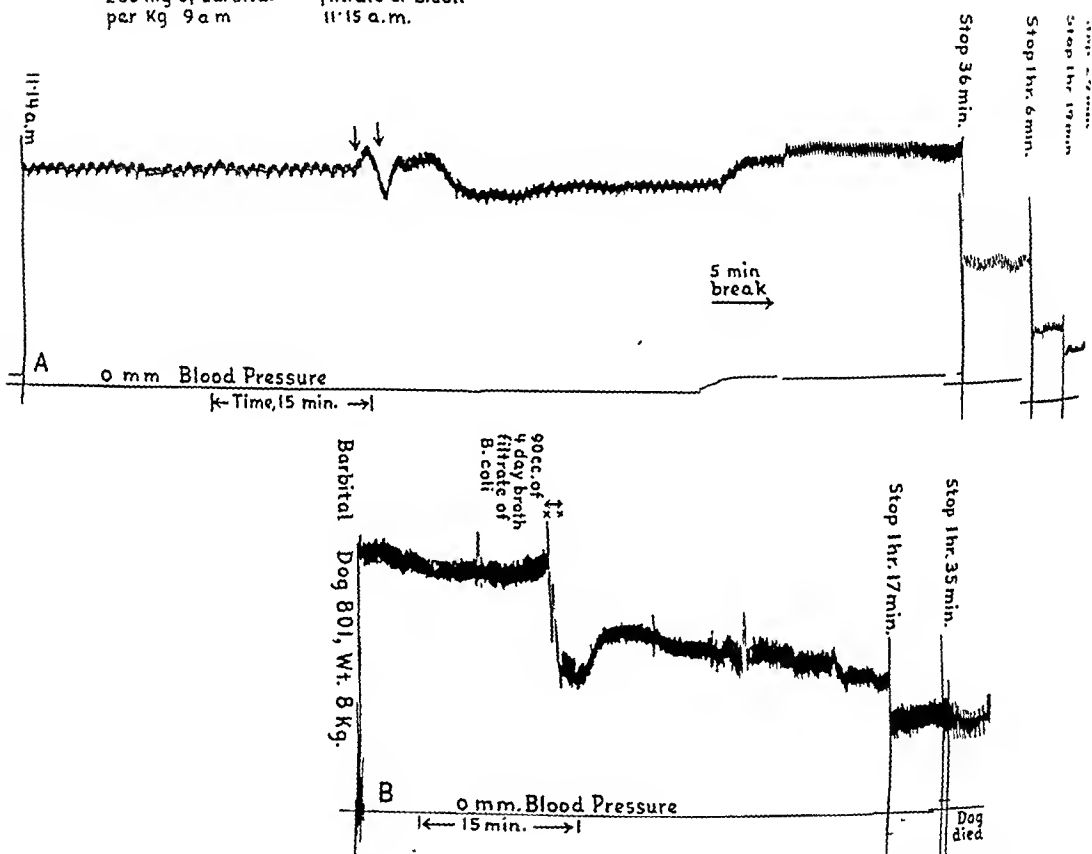


Chart 2.—Tracings showing the effect on the blood pressure of other peptone-free veal infusion broth filtrates of colon bacilli, given intravenously.

Six of the fourteen filtrates of colon bacilli were tested by intravenous injection into unanesthetized rabbits after the method of Steinberg and Ecker⁷ for determining the presence of the "soluble specific substance" of the colon bacillus. All six of them in quantities of 5 cc. produced weakness, diarrhea, collapse and convulsions. Four of six animals succumbed.

In the tests of filtrates from streptococci and staphylococci, there was a slight (average of eight tests 16.5 mm.) delayed drop in blood pressure, but this was not significantly greater than that for the six control animals receiving peptone-free veal infusion broth intravenously (average fall in blood pressure 12.5 mm.). In three instances there was a profound immediate drop in the blood pressure as a

result of the intravenous injection of such products. Two of these three instances occurred when filtrates from twenty day cultures were tested (chart 3). In these latter three instances there was no delayed drop in the blood pressure.

An inquiry into the mechanism of the drop in blood pressure and the shock syndrome so produced was next carried out. Hemoglobin and hematocrit observations were made on dogs receiving such filtrates in conjunction with the blood pressure observations. After the blood pressure had declined to the shock level, the bleeding volume¹⁶ was determined.

It is seen from these observations (table 2) that the average bleeding volume after the intravenous injection of colon bacillus filtrate was 46 per cent of the calculated blood volume. Since the average normal bleeding volume was found to be 58.6 per cent by Roome, Keith and Phemister and 53.4 per cent by one of us (H. N. H.),¹⁷ our findings allow the fall in blood pressure that occurs after the intravenous administration of a filtrate of colon bacillus to be classed as primary shock.

TABLE 2.—*Terminal Bleeding Volume; Associated Changes in Blood Pressure, Cell Volume and Hemoglobin Content After the Intravenous Injection of Colon Bacillus Filtrates*

Dog No.	Weight, Kg.	Berkfeld Filtrate Intravenously	Time from Injection to Death by Bleeding, Hr.	Blood Pressure		Hemoglobin Percentage		Hematocrit Reading		Terminal Bleeding Volume, Percentage of Calculated Blood Volume
				Prior to Bleeding, Initial	Prior to Bleeding, Final	Prior to Bleeding, Initial	Prior to Bleeding, Final	Prior to Bleeding, Initial	Prior to Bleeding, Final	
1P	6.0	50 cc. B. coli-communis (Sw)*	2.0	166	42	84	94	38	45	43
2P	7.5	50 cc. B. coli-communior (St)	5.5	105	112	48	55	52
3P	7.5	50 cc. B. coli-communior (Di)	2.25	124	36	100	122	45	58	33
4P	5.0	50 cc. B. coli-communis (Ja)	8.25	164	40	91	105	46	50	61
5P	8.8	40 cc. B. coli-communior (La)	2.0	164	66	104	106	45	45	35
1002	8.6	43 cc. B. coli-communis (Ja)	1.5	132	52	122	118	51	54	49
1003	8.0	40 cc. B. coli-communior (Di)	2.0	148	54	128	126	53	53	49
Average.....										46

* Laboratory designation of strain.

The significance of such falls in blood pressure is magnified, provided that the action can also be demonstrated after the intraperitoneal administration of the same products. The blood pressure records of four tests are reproduced in chart 4. A drop in blood pressure occurred in each of the four animals but was significant in but one.

Two filtrates from each of five cultures of obligate anaerobic organisms were tested on the blood pressure of dogs. No delayed fall in blood pressure occurred in forty tests on the blood pressure of ten dogs. All the effects observed were

16. Roome, N. W.; Keith, W. S., and Phemister, D. B.: Experimental Shock: The Effect of Bleeding After Reduction of the Blood Pressure by Various Methods, Surg., Gynec. & Obst. **56**:161, 1933.

17. Harkins, H. N.: Bleeding Volume in Experimental Burns, Proc. Soc. Exper. Biol. & Med. **32**:3, 1934.

Dog, wt 8 Kg
260 mg of barbital
per Kg. 12:10 p.m.

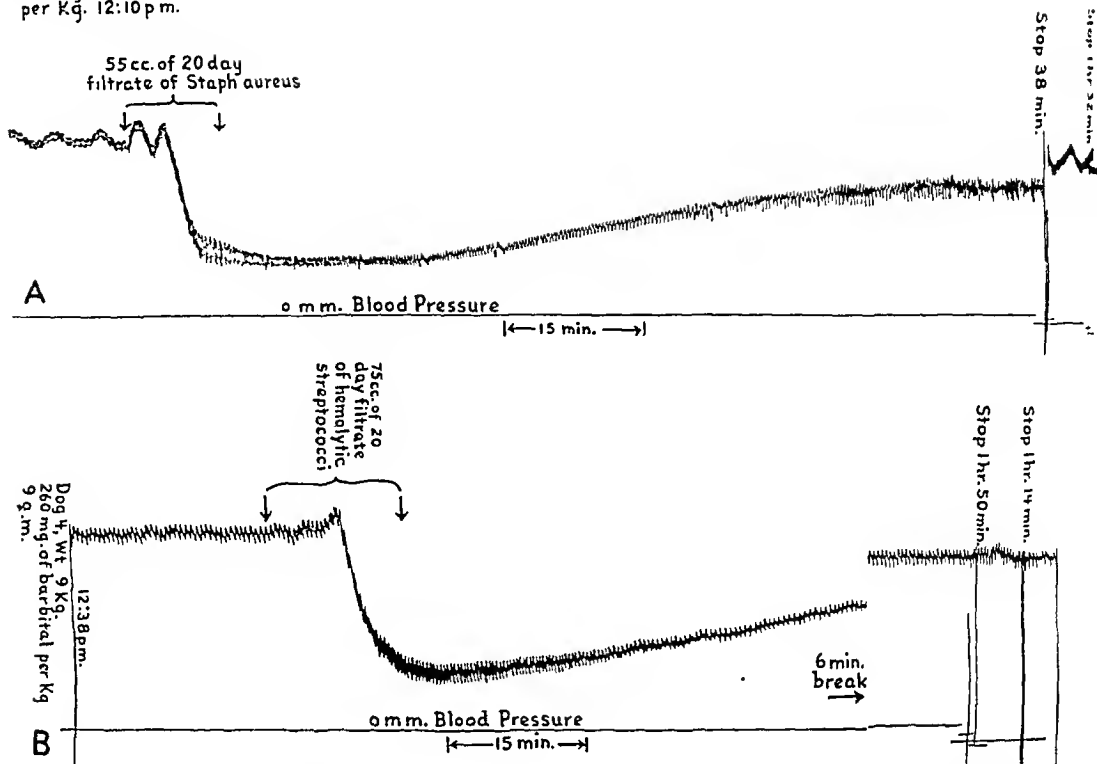


Chart 3.—Tracings showing the effect on the blood pressure of intravenous bacteria-free filtrates. In *A* a filtrate of staphylococci was used, and in *B*, a filtrate of hemolytic streptococci. Note the profound immediate drop with slow recovery in each case.

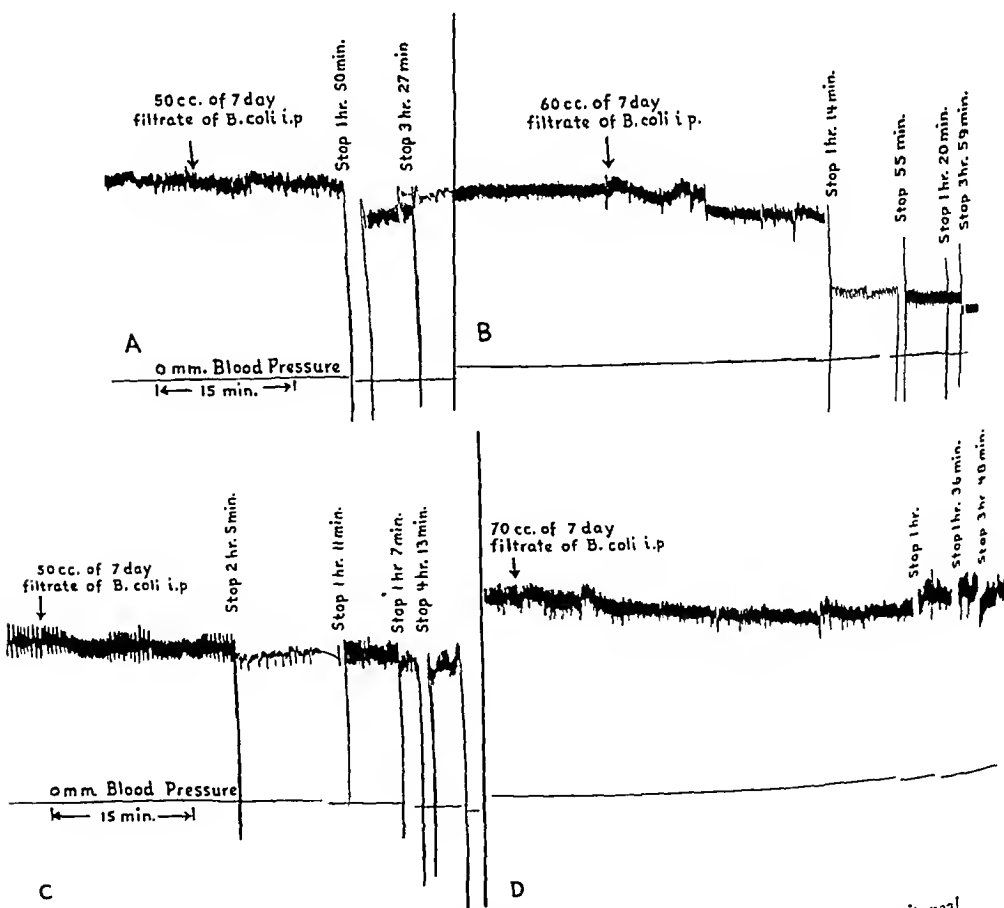


Chart 4.—Tracings showing that vasodepression occurs after the intraperitoneal administration of bacteria-free colon bacillus filtrates. The effect is most pronounced in the upper tracing (*B*).

immediate. Chart 5 is a reproduction of representative blood pressure tracings illustrating the effect of these filtrates. The preparations from *Cl. Chauvei* and from *Vibrio septicus* were devoid of action on the blood pressure, while filtrates from two different cultures of *Cl. Welchii* and from a culture of *Cl. sporogenes* possessed a powerful vasodepressant action. In collateral experiments this same vasodepressant action was demonstrated in rabbits. This effect was also found to persist after atropinization in both rabbits and in dogs.

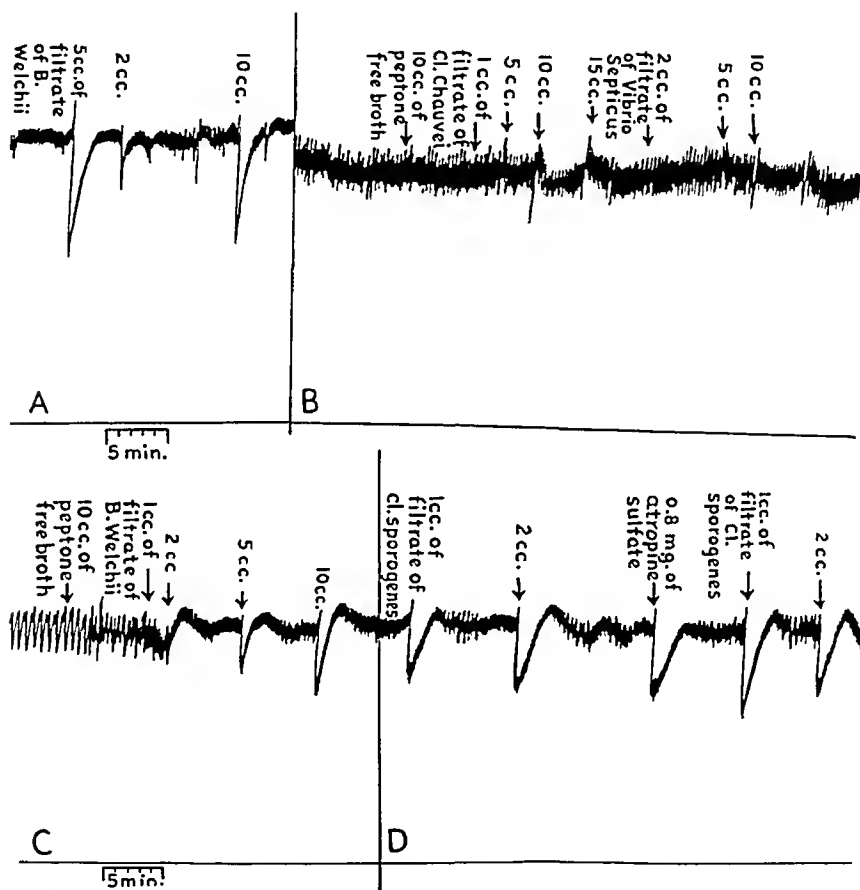


Chart 5.—Tracing showing the effect on the blood pressure of the intravenous administration of bacteria-free filtrates of anaerobic bacilli. In *A* a filtrate of *Cl. Welchii* was used; in *B*, of *Cl. Chauvei* and *Vibrio septicus*; in *C*, of *Cl. Welchii*, and in *D*, of *Cl. sporogenes*.

COMMENT AND SUMMARY

These experiments constitute an inquiry into the nature and origin of the toxic substance present in the peritoneal cavity in experimental suppurative peritonitis. They demonstrate that the substance is not a protein since it occurs in the filtrate after treatment with trichloroacetic acid. Similar extracts of the centrifugated sediments yielded protein-

free filtrates of particular potency. Such a finding points to the cellular abdominal débris, composed of polymorphonuclear phagocytes and adherent material, as being the fraction most potent in the substance. Since similar extracts of washed bacteria were strikingly free from vasodepressant action, it would appear that the substance is a soluble toxin. Its close association with peritoneal cellular débris may indicate either absorption of the toxin to such cells or that the substance is a product of them. Tests of the bacteria-free filtrates from pure cultures of bacteria were included. Even though the symptoms produced by the soluble specific substance of Steinberg and Ecker have been long known, this is the first demonstration that the same bacterial filtrate produces a profound vasodepression. It is possible that the symptoms produced by the soluble specific substance are only those due to the low blood pressure. The close relationship of symptoms to vasodepression is further indicated, as both have an appreciable incubation period following injection before the onset of symptoms. These experiments also demonstrate that certain of the spore-forming obligate anaerobes and staphylococci and streptococci, all organisms associated with suppurative peritonitis, produce soluble vasodepressant substances that appear in bacteria-free filtrates.

The exact rôle that these substances play in an actual instance of peritonitis is not elucidated in these experiments. It is not inconceivable that they could contribute to the final fatal decline in this disease.

CONCLUSIONS

The toxic vasodepressant substance that is present in the peritoneum in many instances of experimental suppurative peritonitis is nonprotein in nature and occurs in greatest concentration in extracts prepared from the centrifugated sediment obtained from peritoneal washings.

The soluble toxic substance present in bacteria-free filtrates of colon bacillus produces a powerful vasodepression after an incubation period following its injection.

The toxic substance from this organism is similarly active after intraperitoneal injection in some instances.

By the bleeding volume method and by observations on cellular and hemoglobin concentration in the blood, the shock syndrome produced by administration of toxic filtrates of the colon bacillus was found to be a primary type, analogous to that produced by the experimental injection of other vascular poisons such as histamine.

Vasodepressant substances with an almost immediate time of action are also produced by the staphylococcus, by strains of streptococci and by cultures of the *Cl. Welchii* and *Cl. sporogenes* that we have examined.

USE OF EXTRAVASATING DYE AS A MEASURE OF SKIN PERMEABILITY TO BAC- TERIAL INVASION

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AND

S. WHEELER

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The subject of disinfection of the skin divides itself naturally into two categories: The first treats of the various chemical or physical means by which the skin is rendered sterile, in other words, the surgical disinfectants, and the second treats of the disinfective power of the skin itself. It is with the latter aspect that this study is concerned.

Colebrook and his co-workers¹ and Arnold² have conclusively shown that the epidermis not only acts as a mechanical barrier against invading organisms but maintains its own indigenous flora and prevents the percutaneous penetration of foreign bacteria. Arnold^{2b} demonstrated that exogenous bacteria and other antigenic substances penetrated into the stratum corneum, where by some unknown process they were either inactivated or destroyed. Tracing the fate of the vanished bacteria in the stratum corneum by the injection of scrapings of keratinized epithelium into animals, he was able to show the presence of their antigens by the recovery of antibodies. Control experiments carried out on the skin of cadavers failed to demonstrate the rapid disappearance of the same organisms.

Other methods of investigating the self-disinfecting property of the skin and determining the presence and degree of percutaneous bacterial invasion have been carried out by Brann³ and Fleming,⁴ who determined the bactericidal effect of cutaneous extracts and other tissues. The percutaneous penetration of antigens has been well established by

From the Laboratory of Surgical Research, Harvard Medical School.

1. Colebrook, L., in Interim Report of Department Committee on Maternal Mortality and Morbidity, London, His Majesty's Stationery Office, 1930, appendix D, p. 132.

2. (a) Arnold, L., and others: *Am. J. Hyg.* **11**:345, 1930. (b) Arnold, L., and Bart, A.: *ibid.* **19**:217, 1934.

3. Brann, G.: *Klin. Wchnschr.* **7**:2059, 1928

4. Fleming, A.: *Lancet* **1**:217, 1929.

Kolle,⁵ Manfredi and Frisco,⁶ Martini,⁷ Hoffmann,⁸ Fränkel⁹ and Hardy, Hudson and Jordan.¹⁰ The criteria used by these investigators for the penetration of bacteria were active systemic disease, positive results of blood culture or demonstrable antibodies. Hallwachs,¹¹ Kasten,¹² Sato¹³ and Matsumoto and Shiraiwa¹⁴ were not uniformly successful in proving this penetration. The discrepancies and their results can perhaps be explained on an increased resistance of the skin to permeation. The work of Arnold implies that the defensive power resides in the stratum corneum, and injuries to it, such as minute abrasions which are incurred in shaving, may increase the permeability of the skin, as has been confirmed by the work of Hardy, Hudson and Jordan.¹⁰

While results in the literature proved suggestive, we felt that the methods used did not afford a very exact evaluation of percutaneous bacterial invasion as an active process. We thus found it necessary in our investigation: (1) to measure the degree and presence of percutaneous bacterial invasion; (2) to determine how rapidly the self-disinfecting power is restored to the shaven skin and (3) to determine if shaving modifies the intracutaneous spread of bacteria.

GENERAL CONSIDERATIONS AND MATERIALS

It is known that local infection alters the capillary permeability in the process of forming inflammation. Induration, edema and erythema are unquestionably derived from the capillaries themselves. It occurred to us that should the capillary blood be colored by a dye, the resulting transudate or exudate would then likewise be colored. Bacterial invasion with subsequent inflammation would result in extravasation of a circulating dye. The advantage of the dye in this case would be that the slightest inflammation would be sharply outlined, whereas a slight degree of erythema under ordinary conditions is difficult to observe and delimit.

5. Kolle, W.: *Ztschr. f. Hyg. u. Infektionskr.* **36**:397, 1901.

6. Manfredi, L., and Frisco, B.: *Centralbl. f. Bakt.* **32**:295, 1902.

7. Martini, E.: *Ztschr. f. Hyg. u. Infektionskr.* **41**:153, 1902.

8. Hoffmann, W.: *Hyg. Rundschau* **13**:114, 1903.

9. Fränkel, C.: *Hyg. Rundschau* **17**:903, 1907.

10. Hardy, A. V.; Hudson, M. G., and Jordan, C. F.: *J. Infect. Dis.* **45**:271, 1929.

11. Hallwachs, W.: *Ztschr. f. Hyg. u. Infektionskr.* **69**:149, 1911.

12. Kasten, F.: *Deutsche med. Wchnschr.* **26**:637, 1903.

13. Sato, K.: *Jap. J. M. Sc. Tr., VII, Social Med. & Hyg.* **1**:175, 1932.

14. Matsumoto, K.; Matsumoto, O. K., and Shiraiwa, T.: *Sc. Rep., Govt. Inst. Infect. Dis., Japan* **6**:145, 1927.

At the suggestion of Dr. John G. Gibson II, of the Peter Bent Brigham Hospital, we employed the blue azo dye T-1824 used by Gregersen and Gibson¹⁵ in the determination of plasma volume. This dye (not listed in the "Color Index") was first used by Dawson, Evans and Whipple.¹⁶

The first indication of the property of this dye to extravasate only where there is increased vascular permeability was noted by Gibson in the course of determining the plasma volume of a patient undergoing fever therapy with diathermy. He observed that the serum contained in a blister caused by an accidental burn was colored blue. Analysis of this fluid in the bleb showed that the ratio of dye concentration to serum protein was identical with that in the blood plasma of the patient. Further observations made by Gibson indicate that this dye, when injected intravenously, enters into some form of combination with serum proteins and that in this combined state it does not permeate the normal capillary wall. He has found that changes in capillary permeability which allow the passage of serum protein through the endothelium also permit the escape of the dye. In short, in the case of the bleb caused by a burn the capillaries at this point were so altered by an irrational phenomenon as to allow the escape of serum proteins together with the dye.

METHOD

In our studies we produced such an irritation to the capillaries of the skin by subjecting them to bacterial invasion. Animals were used in which an excess of dye was in circulation, but in which the skin had not assumed the generalized blue color. One and five-tenths cubic centimeters of the blue azo dye T-1824 (0.5 Gm. per hundred cubic centimeters in saline solution) which had been sterilized was injected into a vein in the margin of the ear of each rabbit twenty-four hours previous to any experiment.

Several series of healthy domestic brown rabbits of the cottontail variety were used. In each instance the abdomen was shaved carefully in order to avoid traumatic abrasions. The skin was then washed with physiologic solution of sodium chloride and with water and subsequently dried.

Standardized eighteen hour broth cultures (p_H 7.4) of *Streptococcus haemolyticus* (beta) were used. In each instance a fresh culture was so prepared that at the time of application to the skin it had been incubated for eighteen hours after the initial seeding of the broth. The same strain of organisms was used throughout the experiments. Two cubic centimeters of this culture was applied with a cotton swab to the shaven skin of a rabbit.

15. Gregersen, M., and Gibson, J.: *Am. J. Physiol.* **50**:113, 1935.

16. Dawson, A. B.; Evans, H. M., and Whipple, G. H.: *Am. J. Physiol.* **51**:232, 1920. The dye is orthotoluidine combined with 2 mols of 1.8 amino 2.4 disulfonic acid. The lot employed in the work was synthesized by the Eastman Kodak Company according to the preparation and directions of Mr. Fieser and Mr. Hartwell, of the Department of Chemistry, Harvard University.

To study variations of intracutaneous spreading of bacteria, a solution containing a substance which we shall call, for purposes of abbreviation, the Reynals factor was prepared from freshly ground testicle. The method was fully described in the reports of the previous investigations by Duran-Reynals¹⁷ and by one of us (M. P.¹⁸).



Fig. 1.—Extravasation of dye and areas of hemorrhage occurring in skin in which the bacteria were applied eighteen hours after shaving. Interval: ten hours after application of organisms.



Fig. 2.—Early extravasation of dye occurring in skin in which the bacteria had been smeared twenty-four hours after shaving. Interval: six hours after application of organisms.

EXPERIMENTAL DATA

Percutaneous Invasion of Streptococci.—Eight rabbits with abdomens carefully shaved were swabbed at various intervals with an eighteen hour broth culture

17. Duran-Reynals, F.: J. Exper. Med. 50:327, 1929.

18. Pijoan, M.: J. Exper. Med. 53:37, 1931.

of *Str. haemolyticus* (beta). In each instance an area of 5 by 10 cm. on the abdomen of the rabbit was uniformly smeared with 2 cc. of this culture. In table 1 are recorded the extent of the lesion and the degree of percutaneous invasion in rabbits shaved at approximately the same time but swabbed at various intervals.



Fig. 3.—Extravasation of dye in skin on which the bacteria were applied thirty-five hours after shaving. Interval: ten hours after application of organisms.

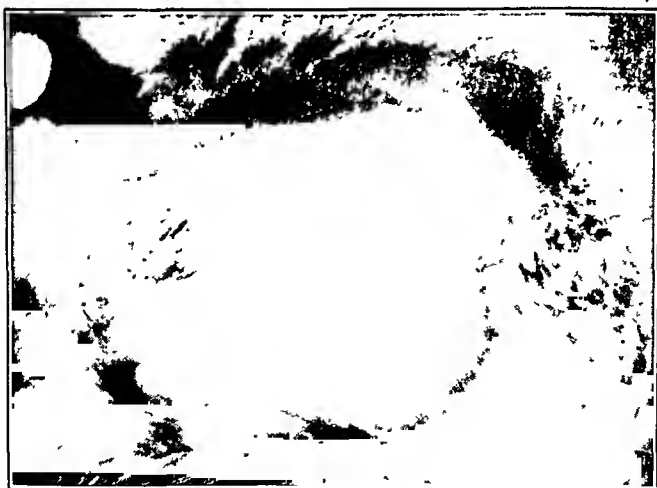


Fig. 4.—Absence of extravasation of dye in skin on which the bacteria were applied forty hours after shaving. Interval: ten hours after application of organisms.

It was further noted that after the extravasation had taken place the blue dye remained fixed in the inflamed tissues, with no appreciable fading. The striking appearance of the dye-stained tissues is clearly shown in the photographs. Controlled experiments with dye and bacteria and skin failed to show that the dye exerted any influence on the course of the inflammation.

Biopsy of stained skin was done in the course of another series of experiments in which the outcome was precisely the same as that presented in table 1. In each instance in which there had been percutaneous bacterial invasion biopsy revealed a typical intracutaneous inflammatory process. From such findings we believe that the presence of blue patches in cutaneous tissues treated with bacteria is a reliable indication of the presence of organisms within those tissues. It appears, therefore, from the experimental data that in a designated shaven area of skin few organisms pass through the already regenerated stratum corneum later than thirty hours after shaving.

TABLE 1.—*Extent of Percutaneous Invasion of Streptococci*

Rabbit No.	Amount of Dye Injected 24 Hours Previously, Cc.	Time Broth Culture of Streptococci Was Smear After Shaving, Hrs.	Degree of Percutaneous Spread*						
			24 Hr.	48 Hr.	72 Hr.	96 Hr.	120 Hr.	144 Hr.	168 Hr.
1	1.5	3	+	++	+++	++++	++++	++++	++++
2	1.5	8	+	+	+++	++++	++++	++++	++++
3	1.5	15	+	+	+	++	++	++	++
4	1.5	24	+	+	+	++	++	++	++
5	1.5	30	±	±	+	+	+	+	+
6	1.5	36	±	±	+	+	+	+	+
7	1.5	48	0	0	0	0	0	0	0
8	1.5	52	0	0	0	0	0	0	0

* + indicates slight extravasation of dye in the tissues; ++, moderate extravasation of dye with noticeable erythema as well; +++, extravasation of dye with erythematous induration, and +++++, extravasation of dye with induration, abscess formation and suppuration.

TABLE 2.—*Extent of Intracutaneous Invasion of Streptococci*

Rabbit No.	Amount of Dye Injected 24 Hours Previously, Cc.	Time of Injection After Shaving, Hr.	Resultant Lesion 30 Hours After Injection of 1 Cc. of 18 Hr. Broth Culture of Str. haemolyticus (beta) plus*		
			0.5 Cc. Saline Solution	0.5 Cc. Muscle Extract	0.5 Cc. Testicle Extract
1	1.5	4	++	++	++++
2	1.5	10	++	++	++++
3	1.5	15	++	++	++++
4	1.5	24	++	++	++++
5	1.5	48	++	++	++++
6	1.5	72	++	++	++++

* + is used as the unit of extent of the lesion as delimited by the dye.

Influence of Shaving on the Intracutaneous Invasion of Streptococci.—A similar series of rabbits were prepared in the same manner as those used in the previous experiments, except that in this series the streptococci were injected intracutaneously instead of being swabbed on the skin. Tissue factors influencing the intracutaneous spread were likewise added in these investigations. The rabbits were shaved on both sides of the abdomen, and three intracutaneous injections made at the same time of the following bacteria: (1) 1 cc. of an eighteen hour broth culture of Str. haemolyticus (beta) in 0.5 cc. of saline solution; (2) 1 cc. of an eighteen hour broth culture of Str. haemolyticus (beta) in 0.5 cc. of supernatant fluid of freshly ground muscle; (3) 1 cc. of an eighteen hour broth culture of Str. haemolyticus (beta) in 0.5 cc. of supernatant fluid of freshly ground testicle.

The results are presented in table 2.

The lesions which occurred in the foregoing experiment were constant in size under the different conditions present, and the interval after shaving had no apparent effect on the extent of the spread of the bacteria introduced intracutaneously. The average area of staining and induration in those lesions which resulted from the injection of broth culture plus saline solution and broth culture plus muscle extract was 1.5 by 1.5 cm., whereas the lesions produced by the injection of broth culture plus testicle extract was 2.5 by 2.5 cm. Injury to the stratum corneum such as occurs in shaving has no apparent effect on the spread of bacteria when they are placed beneath the superficial layers of the skin; furthermore, agents which augment the intracutaneous spread of organisms, such as the Reynals factor, are not modified by shaving.

COMMENT

The selective nature of many dyes is well known. In this case large molecules of blue azo dye T-1824 remains within the circulatory system only to leave it at foci of increased permeability of a vessel. As we have already indicated, there are certain disadvantages in methods previously used to evaluate the reaction of the skin to foreign bacteria. However, we cannot minimize the importance and the results of Arnold² and Colebrook,¹ who succeeded in demonstrating the disappearance of bacteria on the skin by the carefully controlled experiments. We were somewhat unfortunate in attempting to recover organisms in any sort of a quantitative way after the animals had come in contact with their cages. The inevitable contaminations always occurred. Antibody demonstrations and repeated blood cultures are indexes of permeability, but they are too variable to reflect an active process. The method of testing the bactericidal properties of excised skin extracted with alcohol, acetone or ether give interesting results but would seem to lack significance in the face of the evidence that the self-disinfecting power of the skin is a dynamic process with a selective action only on exogenous bacteria. Further observations of Fisher¹⁹ showed that this power varies with the stage of the menstrual cycle, and the investigations of Montgomery²⁰ demonstrated that it is diminished in diabetes.

The dye method is open to criticism. Mainly it may reflect the passage of toxins or lysates through the skin rather than the presence of bacteria themselves. However, organisms were noted in biopsy preparations, and in those cases in which open abscesses developed streptococci could be easily cultured. The dye in itself exhibits no toxic qualities to the epidermal structures.

Our thesis is that shaving increases the susceptibility of the skin to bacterial penetration, possibly owing to minute abrasions caused by the razor on the keratinized epithelium or to a defense process in the horny layer. It seems reasonable to suggest, on the bulk of evidence

19. Fisher, V.: *Proc. Soc. Exper. Biol. & Med.* **28**:952, 1931.

20. Montgomery, B. E.: *Proc. Soc. Exper. Biol. & Med.* **28**:374, 1931.

contributed by other investigators and by our experiments, that shaving before an operation should take place at least thirty hours previous to the incision. This is, of course, with the exception of acute emergencies. It is not denied that after an operation more bacteria penetrate the wound than the surrounding skin, even though freshly shaven, but we suggest that newly shaven skin is more likely to have pathogenic organisms lodged in the cutaneous tissues, and it is through these tissues that the initial incision is made.

CONCLUSIONS

Skin within thirty hours of shaving has an increased permeability to percutaneous bacterial invasion.

Shaving has no effect on the intracutaneous spread of *Str. haemolyticus* (beta).

An azo dye T-1824 employed intravenously delimits the area of bacterial invasion and inflammation by the blue stain it imparts to infected tissues.

JUXTA-ARTICULAR ADIPOSIS DOLOROSA

ITS SIGNIFICANCE AND RELATION TO DERCUM'S DISEASE AND OSTEO-ARTHRITIS

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Generalized adiposis dolorosa is not common, but it is not easily overlooked on account of the universal distribution of the tenderness of the deposits of fat. Localized hypersensitivity of the fat tissues, on the other hand, is common and often remains unrecognized because it is not looked for or is misinterpreted.

The following report concerns a study of cases of localized tenderness of fat around the joints in 112 patients, who were observed within the last six years.

DEFINITION AND SYMPTOMATOLOGY

I apply the term juxta-articular adiposis dolorosa to accumulations of subcutaneous fat around the joints, which are markedly tender to touch or pressure and are not connected with gross alterations of the sensitivity of the overlying skin. The condition occurs most frequently in obese women past middle age. It is usually bilateral, although one side may be affected more than the other. The distribution is characteristic. Most frequently the tender masses of fat are found at the inner sides of the knee joints. Second in frequency are the inner sides of the elbows. Rarely are the outer sides of the ankles and the hips affected. The tender fat is frequently markedly indurated; in other cases distinct lobules are palpated. Frequently the tender fat is not well defined. In some cases, however, small and larger lipomas are distinctly outlined. In many cases the tenderness spreads from the inner side of the knee over to the anterior aspect of the leg and from the inner side of the elbows to the dorsal aspect of the arm. Symptoms of the menopause and an increase in the systolic blood pressure are present in a high percentage of patients. Of the local symptoms exhibited in the extremities, varicose veins, depressed arches, acroparesthesia and vasomotor disturbances and Heberden nodes are frequently found. The complaints for which consultation is requested consist of stiffness and pain or grating in the joints. Examination reveals in a considerable percentage of cases muscular contraction, limitation of motion, chiefly in the shoulder joints, and some deformity and grating in the knee joint.

Roentgenograms in some cases show spur formation or osteophytes at the articular surfaces.

On the basis of these symptoms and findings, the diagnosis of osteoarthritis is usually made. The tenderness found during examination is erroneously interpreted as originating from the capsule or the articular surfaces of the joint, while a careful analysis would have revealed that it is due to hypersensitivity of the subcutaneous fat.

APPEARANCE AND METHOD OF EXAMINATION

Inspection in cases of pronounced involvement reveals bulging masses of fat at the inner sides of the knees, the inner sides of the elbows and the external sides of the ankles and the hips. Sometimes an abrupt decrease in the size of the leg below the knee is noted. On the skin frequently thin spider-weblike veins and sometimes large varicosities are present. The sensitivity of the skin to touch, needle pricks and temperature appears to be normal. The response of the minute vessels and capillaries to histamine also is normal. Neither the appearance of the patient nor the inspection of the skin and the masses of fat gives conclusive evidence for a diagnosis of juxta-articular adiposis dolorosa. Systematic palpation is necessary to discover this condition.

A fold of skin and subcutaneous fat is elevated between the thumb and the other fingers, and gentle pressure is applied. It is necessary to be on guard against hypersensitivity of the skin and misunderstanding on the part of the patient. Therefore, the patient's eyes are best covered, and the sensitivity of the skin is tested previously.

Subcutaneous fat in different parts of the body and the joints are examined as a control. Juxta-articular adiposis dolorosa is diagnosed only when there are centers of tenderness in the characteristic areas around the joints, without changes in the more superficial or deeper structures.

ANALYSIS OF MATERIAL

Several hundred persons with juxta-articular adiposis dolorosa were observed during the past six years in arthritis clinics and in private practice in New York and in Los Angeles. In this paper clinical and laboratory data obtained from a study of 112 of these patients are presented and compiled in table form.

The patients complained of stiffness, pain and disability. Objectively they presented few changes in the joints, such as grating on motion and spurs. In only 1 case was acute infectious arthritis present, and in only 3 was there effusion. In no instance was fibrous and osseous ankylosis noted.

No exact data of the incidence of juxta-articular adiposis dolorosa can be given. Symptoms of this condition were found in from 10 to 15 per cent of my patients with osteo-arthritis seen in various clinics in New York and Los Angeles.

SEX AND AGE INCIDENCE

Sex.—Of the several hundred patients with juxta-articular adiposis dolorosa, only 3 were men. The 112 patients used for this study were women. The occurrence of the condition in men, however, may be more frequent than is indicated in my patients with osteo-arthritis, about 80 per cent of whom were women.

Age.—Table 1 gives the distribution of juxta-articular adiposis dolorosa by decades. The youngest patient was 21 years old; the oldest, 71. Only 4 patients (3.58 per cent) were less than 30. There were 15 patients (12.35 per cent) in the fourth decade. In the fifth decade the

TABLE 1.—*Age Incidence*

Ages	No. of Cases	Percentage
21-30.....	4	3.58
31-40.....	15	12.35
41-50.....	40	35.80
51-60.....	32	30.64
61-70.....	20	17.90
71.....	1	0.89
Total.....	112	

incidence reached its peak, with 40 patients (35.8 per cent), declining in the sixth decade to 32 (30.6 per cent) patients, and in the seventh decade to 20 (17.9 per cent). Nearly two thirds of the patients were therefore between 40 and 60 years of age. About 16 per cent of the patients were under 40 and over 60 years of age. The relation, therefore, to manifestations of the menopause is clearly indicated.

HEIGHT AND WEIGHT RELATIONS

The height of 80 patients is given in table 2. Of these, 28.75 per cent were less than 5 feet (152.4 cm.), 45 per cent were between 5 feet (152.4 cm.) and 5 feet and 2 inches (157.5 cm.) and 23.75 per cent were between 5 feet and 3 inches (160 cm.) and 5 feet and 6 inches (167.6 cm.). Only 1 patient was 5 feet and 10 inches (177.8 cm.) in height.

The weight of 110 patients, clothed but without shoes, was estimated. and the results are in table 3. Only 6.4 per cent of the patients weighed less than 140 pounds (63.5 Kg.); 22.7 per cent weighed between 141 and 160 pounds (64 and 72.6 Kg.), 26.36 per cent between 161 and 180

pounds (73 and 81.6 Kg.), 21.72 per cent between 181 and 200 pounds (82.1 and 90.7 Kg.), 12.6 per cent between 201 and 220 pounds (91.2 and 99.8 Kg.) and 10.8 per cent between 221 and 280 pounds (100.2 and 127 Kg.).

The weight and height relation of 72 patients was compared with the normal values, as compiled in the Medico-Actuarial Mortality Investigation (table 4). Four patients (5.5 per cent) presented values lower than normal. About 10 per cent showed an increase in weight of

TABLE 2—*Height in Eighty Cases*

Feet and Inches (Cm)	No. of Cases	Percentage
4 8 (142.2)	2	2.50
4 10 (147.3)	7	8.75
4 11 (149.8)	14	17.50
5 0 (152.4)	20	25.00
5 1 (154.9)	9	11.25
5 2 (157.5)	7	8.75
5 3 (160.0)	5	6.25
5 4 (162.5)	8	10.00
5 5 (165.1)	1	1.25
5 6 (167.6)	5	6.25
5 7 (170.2)	1	1.25
5 10 (177.8)	1	1.25
Total	80	

TABLE 3—*Weight in Clothes of One Hundred and Ten Patients*

Pounds (Kg.)	No. of Cases	Percentage
111-120 (50.3-54.4)	3	2.72
121-130 (54.9-59.0)	1	0.909
131-140 (59.4-63.5)	3	2.72
141-150 (64.0-68.0)	11	10.00
151-160 (68.5-72.6)	13	11.72
161-170 (73.0-77.1)	11	10.00
171-180 (77.6-81.6)	18	16.36
181-190 (81.6-86.2)	11	10.00
191-200 (86.6-90.7)	13	11.72
201-210 (91.2-95.2)	9	8.17
211-220 (95.7-99.8)	5	4.54
221-230 (100.2-104.3)	7	6.36
231-240 (104.8-108.8)	1	0.909
250-260 (113.4-117.9)	2	1.81
260-270 (117.9-122.5)	1	0.909
270-280 (122.5-127)	1	0.909
Total	110	

less than 20 pounds (9.1 Kg.); about 34 per cent, an increase of between 20 and 40 pounds (9.1 and 18.1 Kg.); over 23.5 per cent, an increase of between 40 and 70 pounds (9.1 and 31.8 Kg.); about 28.5 per cent, an increase of between 70 and 100 pounds (31.8 and 45.4 Kg.), and nearly 3 per cent, an increase of between 120 and 140 pounds (54.4 and 63.5 Kg.). The average increase amounts to about 50 pounds (22.7 Kg.).

BLOOD PRESSURE

The systolic blood pressure was estimated in 50 cases (table 5). In 12 (24 per cent) it was lower than 140 mm. of mercury; in 14 (28 per

cent), between 140 and 150; in 13 (26 per cent), between 150 and 180 and in 11 (22 per cent), between 180 and 220.

Estimation of the systolic blood pressure in relation to age gives an increase over normal average values in 41 cases (82 per cent) and lower values in 9 cases (18 per cent). The average increase in systolic pressure amounted to 23.6 points. In 25 of the 50 cases (50 per cent) the diastolic pressure showed an increase over normal values and in 23 cases (46 per cent) a decrease; in 2 cases (4 per cent) the diastolic

TABLE 4—*Deviation from the Normal Weight in Seventy-Two Cases**

Increase in Pounds (Kg.)	Number of Cases	Percentage	Decrease in Pounds (Kg.)	Number of Cases
5 10 (2 3 4 5)....	1	1.47	7 (3 2)	1
10 19 (4.5-8 6)....	6	8.81	10 20 (4 5 9 1)	3
20- 29 (9.1-13 2)....	9	13.23		
30- 39 (13 6-17.7)...	14	20.59	Total	4
40- 49 (15 1-22 2)....	5	7.35		
50 59 (22.7-26 8)....	5	7.35		
60 69 (27.2-31 3)....	6	8.81		
70- 79 (31.8-35 8)....	8	11.76		
80 89 (36 8-40 4)....	7	10.30		
90 100 (40 8-45 4)....	5	7.35		
120 129 (54 4-58 5)...	1	1.47		
130 139 (59 63).....	1	1.47		
Total	68			

* The standard of normal weights at different ages and heights is adopted from the report from the Medico-Actuarial Mortality Investigation.

TABLE 5—*Systolic Blood Pressure in Fifty Cases*

Mm. of Hg	No. of Cases	Percentage
100-109..	2	4
110-119...	2	4
120-129 ..	4	8
130-139..	4	8
140-149 ..	14	28
150-159...	4	8
160-169...	6	12
170-179 .	3	6
180-189 ...	6	12
190-199....	1	2
200-209	2	4
210-220 .	2	4
Total	50	
Average increase, 23.6 mm. of Hg		

pressure was normal. The average decrease was about 6 points below normal. The diastolic pressure, therefore, showed only a small deviation from the normal.

The pulse pressure showed an increase over normal in 44 cases (88 per cent) and a decrease in 6 cases (12 per cent). The average increase for the series was about 21 points, which is almost identical with the increase in systolic pressures. The increase in blood pressure in these cases, therefore, is characterized by the elevation of the systolic blood pressure in 82 per cent. A marked increase, however (over 180 mm. of mercury), was found in only 18 per cent.

MENSTRUATION AND CHILDBIRTH

Table 6 gives data concerning the menstruation in 89 cases. Twenty-four (27 per cent) of the women still had menstrual periods. Seventeen of these had periods of a normal character, and in 5 (21 per cent) the flow was scanty or irregular. The menstruation was profuse in only 2 (8 per cent). Of the 65 women (73 per cent) in menopause, 17 (26 per cent) ceased menstruating before the age of 40; 12 of these were castrated. Twenty-six (40 per cent) stopped menstruating between 40 and 45 years of age; 4 of these were castrated. Seventeen (26.15 per cent) ceased menstruating between 45 and 50 years of age; 1 of these was castrated. Surgical menopause was induced in 17 women, or about 18 per cent of the total group, or over 26 per cent of those in menopause. Of a smaller group of patients in whom the condition was of recent origin, surgical menopause was induced in about 45 per cent. The frequency of surgical intervention and the fact that about two

TABLE 6.—*Data on Menstruation in Eighty-Nine Cases*

Menopause*	Number of Cases	Percentage	Type of Menstruation	Number of Cases	Percentage
Under 40.....	17	26.15	Profuse.....	2	8.33
40-45.....	26	40.00	Irregular.....	2	8.33
45-50.....	17	26.15	Scanty.....	3	12.50
50-55.....	1	1.54	Normal.....	17	70.83
Uncertain.....	4	6.15			
Total.....	65		Total.....	24	

* Surgical menopause was produced in 17 cases (26.15 per cent). Sixty-five (73 per cent) women were in menopause; menstruation was present in 24 cases (27 per cent).

thirds of the patients with juxta-articular adiposis dolorosa were women in menopause emphasize the etiologic significance of the ovarian dysfunction.

Data on childbirth were noted in the histories of 52 patients. Forty-one (79 per cent) of the women were multiparas, 3 (5.8 per cent) had 1 child and 8 (15 per cent) had no children. This prevalence of multiparas was also found among the women with generalized adiposis dolorosa (Dercum's disease).

ONSET OF SUBJECTIVE SYMPTOMS IN THE EXTREMITIES

The development of hypersensitive fat pads, generally not being accompanied by pain, is noticed only by a minority of patients who pay close attention to the shape of their limbs. These occasionally consult a physician for painful "bumps over the joints." As a rule, the presence of the hypersensitive deposits of fat is discovered in the course of consultation for pain, stiffness or grating in the limbs. Table 7 gives the duration of these complaints in 65 patients. In 36 (55.4 per cent), the duration of symptoms amounted to from one to twenty-five years.

In 29 (44.9 per cent) the subjective symptoms were of less than one year's duration. This gives one an opportunity to discover the localized adiposis dolorosa comparatively early. About 94 per cent of the patients were seen by a physician within three years after the onset of symptoms.

DISEASES AND OPERATIONS DURING ADULT LIFE

Eighty-one of the patients gave a history of preceding disease (table 8). Fourteen (17.3 per cent) had diseases referable to, and operations on, the sexual organs. Nine (11.1 per cent) had undergone appendectomy, and cholecystectomy had been performed on an equal number. One patient (1.2 per cent) each suffered from gastric ulcer and cancer of the stomach, respectively. Therefore, 29.6 per cent had diseases of the abdominal organs. In addition, 12 suffered from hemorrhoids (14.7 per cent). Injuries and diseases of the joints unrelated to the present complaints were found in 7 patients (8.6 per cent). Acute infectious

TABLE 7.—*Duration of the Onset of Symptoms in Sixty-Five Cases*

Duration	No of Cases	Percentage
Less than one year.	29	44.6
1-2	10	15.4
2-3	5	7.7
3-4	11	16.7
4-5	1	1.5
5-6..	3	4.6
6-10	3	4.6
10-20	3	4.6
Total	65	

polyarthrititis was present in 1. A history of phlebitis was given by 4 patients (4.9 per cent), and only 1 patient had suffered from exophthalmic goiter. Three patients gave a history of syphilitic infection. The Wassermann reaction was negative in 2. Mild diabetes was found in 1.

ORAL FOCI OF INFECTION

The condition of the tonsils was noted in 41 patients. Some degree of inflammation was found in 10 (24.4 per cent). The tonsils were normal in 16 (39 per cent), and 5 (12.2 per cent) had undergone tonsillectomy.

The condition of the teeth was noted in 53 patients. Twenty-eight (52.8 per cent) had used plates for years, and 6 had more or less extensive bridge work. Seventeen (32 per cent) had diseased teeth or pyorrhea, and 8 (15.1 per cent) had normal teeth. The percentage of oral infection in this series of patients does not exceed that usually found in persons of the same age and social environment. Therefore, no conclusions as to the relations of oral infection to the development of juxta-articular adiposis dolorosa can be drawn.

ENDOCRINE DISTURBANCES

The majority of the patients showed symptoms of menopause, consisting of hot flushes, headaches, dizziness, nervousness and hypothyroidism, especially thick, dry skin, scanty hair, low basal metabolic rate and characteristic distribution of obesity. In 1 patient this was due to hypothyroidism after thyroidectomy for exophthalmic goiter.

A high degree of endocrine disturbance was found in 10 patients (8.9 per cent). Of these, 4 showed symptoms of pluriglandular disturbances (hypofunction of the ovaries, pituitary and thyroid). One had decalcification of the skeleton, with a calcium content of the blood of 11.8 mg.

TABLE 8.—*Preceding Diseases and Operations During Adult Life**

Disease and Operation	No. of Cases	Percentage	Comment
Typhoid.....	2	2.4	
Diphtheria.....	1	1.2	
Syphilis.....	3	3.7	
Nephritis.....	1	1.2	Wassermann reaction negative in 2 and positive in 1
Myocarditis.....	2	2.4	
Apoplexia.....	2	2.4	
Eczema.....	4	4.9	
Psoriasis.....	1	1.2	
Exophthalmic goiter.....	1	1.2	Thyroidectomy 10 years pre- viously
Diabetes.....	1	1.2	
Glaucoma.....	1	1.2	
Pulmonary tuberculosis.....	1	1.2	
Gastric ulcer.....	1	1.2	
Cancer of stomach.....	1	1.2	
Cholecystectomy.....	9	11.1	
Appendectomy.....	9	11.1	
Hysterectomy and ovariectomy.....	14	17.3	
Phlebitis.....	4	4.9	
Hemorrhoids.....	12	14.7	
Facial paralysis.....	1	1.2	
Herpes zoster.....	1	1.2	
Injuries to joints.....	3	3.7	
Other joint diseases.....	4	4.9	
Sciatica.....	1	1.2	
Rheumatic fever.....	1	1.2	
Total.....	51		

* The data were not complete in a number of cases. Oral foci of infection are discussed separately.

per hundred cubic centimeters, indicating hyperparathyroidism. The basal metabolic rate of 14 patients was estimated; 35.7 per cent showed a minus deviation from normal higher than minus 10. The cholesterol content of the blood of 16 patients was estimated, and 9 (56.2 per cent) presented values over 275 and as high as 375. This marked hypercholesteremia is added evidence of dysfunction of the thyroid glands and is discussed under the laboratory findings. In 6 patients the sella turcica was examined roentgenographically (see table 14); it was found to be normal in 2, large in 2, small in 1 and irregular in 1.

One patient showed calcification of one adrenal gland. The disturbances of the endocrine glands in the majority of patients were not of the type which are associated with hereditary or acquired gross pathologic changes. The largest number of patients were middle-aged

multiparas, and chronic wear and tear of the glands of internal secretions appears to be the significant factor in the production of juxta-articular adiposis dolorosa.

That this symptom complex may, however, develop also on the basis of congenital dysfunction of the endocrine glands is illustrated in the following case.

E. P., aged 19, Jewish, measuring 6 feet (182.8 cm.) in height, weighing 205 pounds (93 Kg.), complained that seven weeks before the present examination, while dancing, he twisted his left leg and collapsed. The knee began to swell, and a contraction developed. He improved under physical therapy, but four weeks later he hit the knee against the dashboard of an automobile. It became more painful, contracted and swollen. He had swelling and locking of the right knee joint. He continued to suffer from attacks of locking in the knee joint and sometimes felt a loose body, which he replaced by manipulation. A diagnosis was made of loose cartilages bilaterally.

The patient had been stout since childhood and suffered from pain and disability of the feet and legs. A diagnosis of a pituitary disturbance was made, and he was given pituitary extracts for several years.

Examination revealed a youth of above normal height and weight, with large extremities and irregular teeth. The left knee was flexed about 120 degrees. It was deformed, but there was no fluctuation at the time of examination. The fat pads at the inner sides of the knee joints were hypersensitive. Roentgenograms made at the age of 13 showed an irregular epiphysis at the metacarpal bones. At the age of 15 the left knee joint showed osteochondritis dissecans at the inner side of the lateral condyle of the femur. In addition to these findings, the roentgenograms showed spurs over the condyles of the tibia; the femur and the articular surfaces of the patella appeared to be highly irregular. The infrapatellar fat pad was very much enlarged.

Laboratory examination showed a sedimentation rate of 7 mm., a hemoglobin content of 90 and 6,200 white cells and 5,025,000 erythrocytes.

The loose body was removed by operation; the enlarged fibrous and inflamed fat pad was resected.

Diagnosis and Résumé.—The patient, a youth of 19 who since childhood had had symptoms of a pituitary disturbance, had juxta-articular adiposis dolorosa. The bones and joints showed spur formation characteristic of osteo-arthritis, usually met only in advanced age.

LABORATORY FINDINGS

In the cases in this series the urine was found to be normal on routine examination, except for the frequent occurrence of traces of albumin. Pus cells and epithelial cells from the bladder and vagina were found in the sediment; in some cases there were also red blood corpuscles. Traces of sugar were found in only 1 case. The examination of the blood for the sugar content in a small number of cases gave results below 100 mg. per hundred cubic centimeters, with the exception of 2 cases in which it was 118 and 140 mg.

The hemoglobin content ranged from a minimum of 62 per cent to a maximum of 100 per cent, with an average of 84 per cent; the blood counts showed erythrocytes (minimum 4,000,000, maximum 6,000,000, average 4,800,000), leukocytes (minimum 5,000, maximum 9,500, average 7,000), polymorphonuclear leukocytes (minimum 36 per cent, maximum 71 per cent, average 58 per cent), lymphocytes (minimum 25 per cent, maximum 60 per cent, average 34.4 per cent) and eosinophilic leukocytes (minimum 1 per cent, maximum 1.5 per cent, average 1.2 per cent).

The blood counts, therefore, did not reveal a conspicuous deviation from normal.

BLOOD SEDIMENTATION RATE

The sedimentation rate of the blood corpuscles was estimated in 50 cases (table 9). The Westergren method was used in 34 and the Linzenmeier method in 16, the values obtained by the latter method being

TABLE 9.—*Blood Sedimentation Rate in Fifty Cases**

Mm.	No. of Cases	Percentage
1-14.....	17	34
15-25.....	14	28
26-40.....	15	30
41-60.....	4	8
Total.....	50	

* In 34 cases, the Westergren method, giving the sedimentation of red corpuscles in millimeters after one hour, was used. In 16 cases the method of Linzenmeier was used, which estimates the time necessary for the corpuscles to sink to a level marked 18 mm. on the special tube. The results then were computed to conform to the values obtained by the Westergren method.

computed to conform with those obtained by the Westergren method. Although 10 mm. is generally given as the high normal value of sedimentation with the Westergren method, in women I consider sedimentation up to 15 mm. in one hour as the limit of the normal on account of the frequency of physiologic processes, especially the menstrual cycle, which tend to elevate the sedimentation rate in normal women.

In only 34 per cent of the cases was the sedimentation rate found to be lower than 15 mm. In 66 per cent the sedimentation rate was increased. In a previous study of the comparative sedimentation rate of blood corpuscles in synovial fluid and blood plasma, I¹ called attention to an increase in the sedimentation rates in a high percentage of cases of osteo-arthritis (over 62.4 per cent). In the presence of effusion the sedimentation rate was increased in fully 82.4 per cent of the cases. In the cases of juxta-articular adiposis dolorosa, which condition is generally confused with osteo-arthritis, there was a prevalence of sedimen-

1. Kling, David H.: Sedimentation Rate of Blood Corpuscles in Synovial Fluid and in Plasma, Arch. Int. Med. 50:419-434 (Sept.) 1932.

tation values which were higher than normal. The value, therefore, of the sedimentation tests for differentiation between osteo-arthritis and infectious arthritis is limited. The presence of an increased sedimentation rate in localized adiposis dolorosa points either to infectious foci or to an underlying unbalanced equilibrium of the body fluids (a high globulin, fibrinogen or cholesterol content of the plasma).

BASAL METABOLIC RATES

The basal metabolic rate was estimated in 14 cases (table 10). In 8 the values were in the normal range with minus and plus values between 1 and 9. In 3 there was a slight diminution of the basal metabolic rate between 10 and 14 and in 1 a value of plus 12. In only 2 cases (13.3 per cent) was a marked diminution of minus 21 and minus 26, respectively, present. The basal metabolic rate was decreased in only 33 per cent of the cases.

TABLE 10.—*Basal Metabolic Rates in Fourteen Cases*

Deviation	No. of Cases Minus	No. of Cases Plus
0-9.....	4	4
10-14.....	3	1
21.....	1	0
26.....	1	0
Total.....	9	5

BLOOD CALCIUM

The calcium content of the blood was estimated in 15 cases (table 11). In only 1 case was there a marked decrease in the calcium content of 9.2 mg. per hundred cubic centimeters. In 6 cases the calcium values were slightly lower than normal—from 9.6 to 9.9 mg. In 6 cases normal values, between 10 and 10.3 mg., were found. In 1 case the calcium content was 11.1 mg. In this case the roentgenogram did not show a decalcification of the skeleton. In 1 case the calcium content was 11.8 mg., and the roentgenogram showed marked decalcification of the long bones, indicating a possible hyperparathyroidism.

CHOLESTEROL

The cholesterol content of the blood (table 12) was estimated by the modified Bloor method in 16 cases. The normal values in this laboratory are between 160 and 200 mg. per hundred cubic centimeters. In only 2 cases were the values within this range of the normal. In 5 cases (31 per cent) the cholesterol content varied from 200 to 250 mg.;

in 4 cases (25 per cent), from 275 to 300 mg. In 5 cases (31 per cent) there were markedly high values of between 300 and 375 mg.

In the absence of diabetes and nephritis, the elevation of the cholesterol content appears to be due partly to arteriosclerosis and partly to hypofunction of the thyroid. In the majority of cases in which hyperthyroidism was present the cholesterol content was decreased, and in those in which there was hypothyroidism it was increased. The regulating influence of the thyroid on the cholesterol has been established by a number of investigators. Schally² found evidence that not only quantitative changes in the function of the thyroid but qualitative changes are expressed in changes of the cholesterol content

TABLE 11—*Blood Calcium Content in Fifteen Cases*

Mg. per 100 Cc of Blood	No. of Cases	Percentage
9.2	1	6.6
9.6-9.9	6	39.6
10-10.3	6	39.6
11.1.	1	6.6
11.8	1	6.6
Total	15	

TABLE 12—*Cholesterol Content of the Blood in Sixteen Cases*

Mg. per 100 Cc of Blood	No. of Cases	Percentage
170-199	2	12.5
200-224	4	25.0
225-249	1	6.2
275-299	4	25.0
300-324	1	6.2
325-350	2	12.5
357-375	2	12.5
Total	16	

of the blood. The latter is therefore a more sensitive indicator of the status of the function of the thyroid than the basal metabolic rate, which indicates only quantitative changes. This is corroborated in this series of cases, in the majority of which there were clinical symptoms of hypothyroidism. The basal metabolic rate, however, was decreased in only 33 per cent, while the cholesterol content of the blood was increased in fully 88 per cent. However, this increase in the cholesterol content was found not only in cases of juxta-articular dolorosa but also in a high percentage of cases of osteo-arthritis. Indeed, I regard abnormally high cholesterol values as the important finding of the blood chemistry in cases of osteo-arthritis.

2. Schally, A. O. Störung und Regulation des Cholesterinstoffwechsels. Schilddrüse und Cholesterinstoffwechsel, *Ztschr. f. klin. Med.* 128:376-386, 1935

The circulation in the arterioles and capillaries of the skin over the tender fat masses was tested after the method of Starr.³ The skin was pricked with a needle, and a drop of 1 per cent histamine acid phosphate was applied. The response was normal, as evidenced by development of a wheal and flare within five minutes. In some cases the wheal was reddish instead of the normal white color.

SYMPTOMS IN THE EXTREMITIES AND JOINTS

The subjective symptoms consisted of pain, weakness, stiffness, a feeling of cold and paresthesia in the extremities. They were corroborated by objective findings in 44 cases (39.3 per cent) as follows: rough grating and the formation of spurs, 24 cases (19.5 per cent); increase of infrapatellar fat pad, 12 cases (10.6 per cent); fine grating,

TABLE 13—Location of Subjective and Objective Symptoms of the Joints *

Location	No of Cases	Percentage
Knees.	50	44.6
Knees and spine	7	6.2
Knees and hips	3	2.7
Knees and fingers	5	4.4
Knees, ankles and legs	13	11.6
Knees, ankles and arms	4	3.6
Knees, arms and hands	3	2.7
Toes and fingers	4	3.6
Ankles	3	2.7
Hips	9	8.0
Elbows	2	1.8
Wrists....	2	1.8
Sternoclavical	1	0.9
Shoulders	3	2.7
Several joints other than knees	3	2.7
Total	112	

* Pain, paresthesia, weakness, swelling, grating or deformity

5 cases (4.4 per cent), and effusions, 3 cases (2.6 per cent). In the remaining 70 cases (60.7 per cent), no objective findings were present in the joints.

The distribution of both subjective and objective symptoms is given in table 13. In 50 cases (44.6 per cent), the knees alone were involved; the knees and other joints were the seat of the painful deposits of fat in 35 (31.15 per cent). The knees therefore were involved in 85 cases (76 per cent).

DEPRESSED ARCHES AND VARICOSE VEINS

Weak feet were found in 53 cases (56.2 per cent) and varicose veins in 57 (51.7 per cent). In the majority of instances they were not very large. The presence of minute veins which branched off in different

3 Starr, J, Jr. Change in Reaction of Skin to Histamine as Evidence of Deficient Circulation in Lower Extremities, J A M A 90:2092-2094 (June 30) 1928.

directions over the painful deposits of fat was characteristic. The prevalence of depressed arches and varicose veins indicates the type of person who develops juxta-articular adiposis dolorosa. Secondly, it may have indirectly an etiologic relation. The static strain of the weak feet, causing tiredness, leads to insufficient exercise, which increases the body weight and diminishes the circulation in the limbs. This in turn aggravates the varicose veins, thus further impairing circulation and malnutrition of the tissues. Finally, also, the pressure of the deposits of fat impedes the flow of blood. A vicious circle is in this way formed and maintained.

TABLE 14.—*Roentgenographic Picture*

Joints Involved	No. of Cases	Normal	Percentage	Pathologic Picture	
Knees.....	28	7	25.0	Spurs on the articular surfaces.....	16
				Hypersensitive fat.....	2
				Calcified quadriceps tendon.....	1
				Calcified meniscus.....	1
				Loose body in knee.....	1
				Total.....	21
Shoulders.....	6	2	33.3	Subacromial bursitis.....	2
				Calcified acromial spur.....	1
				Deformed tuberosity of humerus...	1
				Total.....	4
Elbows.....	1	0	Periostitis of epicondyle.....	1
				Total.....	1
Fingers.....	4	1	25.0	Spur at phalangeal joint.....	2
				Destruction of phalangeal joint....	1
				Total.....	3
Spine.....	6	2	33.3	Spurs.....	4
				Total.....	4
Totals.....	45	12			
Sella turcica.....	6	2	33.3	Two large, one small and one irregular	

ROENTGENOGRAPHIC FINDINGS

Roentgenograms of the joints or spine were made in 45 cases in which the clinical findings supported the complaints of the patients and in which hypersensitivity of the fat was marked. The results are presented in table 14.

Of 28 roentgenograms of the knees, 7 (24.6 per cent) were normal. Of the 21 cases in which pathologic changes were pictured, hypertrophic fat pads were visualized by inflation of air into the joints in 2 (17.4 per cent). In 1 case there was calcification of the quadriceps tendon. In only 16 cases was degeneration of the articular surfaces present, as evidenced by spur formation of the patella, tibia or femur. In 1 case loose bodies were found.

The changes of the articular surfaces, therefore, were in the majority of the cases not of a nature that of necessity produces symptoms. In a

large number control roentgenograms of patients past middle age showed identical changes at the articular surface without symptoms of osteoarthritis.

In roentgenograms which showed the soft tissues plain, the enormous increase and cufflike overlapping of the fat masses around the joints were visualized. It was evident that in marked flexion these masses of fat suffer pressure and in consequence give rise to painful sensations (fig. 2).

PATHOLOGIC CHANGES

Biopsy was performed on the hypersensitive fat pads and on overlying skin at the inner side of the knees in 6 cases. Five times small strips of skin and fat about 1 inch (2.5 cm.) in size were removed. In 1 case (see case 1) a large mass of fat was excised from the inner side of the left knee, through an incision about 3 inches (7.6 cm.) long. Grossly the skin appeared normal and the fat was yellowish, and in few cases it was more resisting than normal. The tissues were preserved in formaldehyde and embedded in paraffin. The sections were stained with hematoxylin and eosin and also with special nerve stains made by Dr. Cyrill B. Corville. In all sections the epidermis appeared to be normal. The corium consisted in some sections of loose collagenous fibers and in other sections of denser collagenous fibers. Blood vessels were prominent in some sections, but only few showed sclerotic changes. The fat was of the large vacuole type. In some sections the interlobular fibers were thickened. Several small and large nerves were seen in the fat and corium and appeared to be normal. The minimal changes do not throw a light on the cause of the hypersensitivity of the fat. Interstitial inflammation of the nerves which were found by Dercum⁴ and other observers in generalized adiposis dolorosa were not found by the method of examination in the 6 cases in this series. It must, however, be borne in mind that Page⁵ and others have found the fat in generalized adiposis dolorosa to be normal histologically and chemically. It is possible that the mere increase of the fat tissue and the accompanying increase in blood supply causes pressure on the nerves and is responsible for the symptoms of hypersensitivity. Increase in the tension of the tissues is evidenced by the frequently found induration of the hypersensitive fat tissues.

4. Dercum, F. X.: A Case of Subcutaneous Connective Tissue Dystrophy, *University M. Mag.* **1**:140, 1889; Three Cases of Hitherto Unclassified Affection Resembling in Its Grosser Aspects Obesity, But Associated with Special Nervous Symptoms: Adiposis Dolorosa, *Am. J. M. Sc.* **104**:521, 1892.

5. Page, Irvine H.: Chemische Untersuchungen bei der Dercumschen Krankheit, *Virchows Arch. f. path. Anat.* **279**:262-264, 1930.

LOCALIZATION OF THE HYPERSENSITIVE FAT DEPOSITS

The inner side of the knee alone was found to be hypersensitive in 45 cases (40.2 per cent); in 9 of these (8 per cent) only one knee was hypersensitive (table 15). In the majority of these cases the anterior aspect of the leg over the tibia was also found to be hypersensitive. In 53 cases the inner sides of the knees and the fat pads around other joints were tender (47 per cent). The most common combination was tenderness of the inner sides of the knees and elbows in 29 cases (26.2 per cent); next, the inner sides of the knees and the outer aspects of the ankles in 15 cases (13.4 per cent). The elbows alone were hypersensitive in 1 case, the ankles in 2 and the thighs in 3. Hypersensitiveness of the inner sides of the elbows usually spread to the dorsal aspects of the arms. The knees were involved in 107 cases (95.5 per cent) and should therefore be investigated first, followed by the elbows and the outer sides of the ankles. Indeed, one can predict from the degree of hypersensitivity on the inner sides of the knees the involvement of the other regions. Transition to generalized adiposis dolorosa was found in 3 cases in which the knees and elbows and the outer sides of the thighs were found to be hypersensitive.

TABLE 15.—*Location of Hypersensitive Masses of Fat*

Location	No. of Cases	Percentage
One knee.....	9	8.0
Both knees.....	45	40.2
One knee and elbow.....	4	3.6
Knees and elbows.....	29	26.2
Knees and gluteal region.....	2	1.8
Knees, elbows and gluteal region.....	3	2.7
Knees and ankles.....	15	13.4
Elbow.....	1	0.9
Ankles.....	2	1.8
Gluteal region.....	2	1.8
Total.....	112	

THERAPY

All therapeutic measures were usually combined with a reducing diet. They were directed against the complaints and symptoms of the patients as well as against the hypersensitivity of the juxta-articular fat. The modalities of therapy and the results in 70 cases are tabulated in table 16.

In 48 cases (68.6 per cent) no decrease of sensitivity was noticed. In 22 (31.4 per cent) physical therapy was given. It consisted in baking or diathermia, with massage, in 12 cases. There was improvement in only 1 case. Short and ultrashort wave therapy was applied in 3 cases, with decrease of hypersensitivity in 1. In 6 cases histamine cataphoresis was applied to the hypersensitive fat pads. I have described

the technic of this new therapy elsewhere.⁶ In 5 cases, a decrease of hypersensitivity was noticed immediately after treatment. However, it persisted for only a short time. Finally, roentgen treatment was given in 3 cases, with improvement in 1.

In 41 cases general measures were applied: Iodine preparations were given in 7 cases and a foreign colloidal iodine preparation for intramuscular injection was given in 6, without effect. In 1 case, iodine and colchicine were injected intravenously, with a decrease in the sensitivity of the fat pads. In 21 cases Crowe's streptococcus vaccine was given subcutaneously, with a decrease in hypersensitivity in 1 case.

Endocrine preparations were used in 30 cases. In 19 ovarian products were administered either by mouth or by injection. In 5 diminution of sensitivity of the fat pads was noted. Thyroid was given in 14 cases. In 3 it had to be discontinued on account of toxic symptoms.

TABLE 16.—*Therapy Employed in Seventy Cases*

Therapy	No. of Cases	Improved	Percentage	Not Improved	Percentage
Baking or diathermia with massage....	12	1	8.1	11	91.7
Short and ultrashort wave diathermia.	3	1	33.3	2	66.6
Histamine cataphoresis.....	6	5	83.3	1	16.6
X-ray therapy.....	3	1	33.3	2	66.6
Injections of saline and procaine hydrochloride solutions.....	4	1	25.0	3	75.0
Injections of iodine preparation*.....	6	0	6	100.0
Injections of iodine and colchicine.....	1	1	100.0	0	
Streptococcus vaccine.....	4	2	50.0	2	50.0
Ovarian preparations.....	19	5	26.3	14	73.7
Thyroid.....	11	4	36.3	7	63.6
Excision.....	1	1	100.0		
Totals.....	70	22		48	

* An imported colloidal iodine preparation.

Of the remaining 11 cases, $\frac{1}{4}$ grain (0.016 Gm.) of desiccated glands was given daily in 1 and from $1\frac{1}{2}$ to 3 grains (0.097 to 0.195 Gm.) in the others for a period of from three to sixteen months.

The hypersensitivity of the juxta-articular fat pads was markedly decreased in 4 cases. In 7 the result was entirely negative. In 4 cases 25 cc. of a 0.1 per cent solution of procaine hydrochloride in saline solution gave beneficial results in 1 and negative results in 3. In 1 case, the fat pad at the inner side of the left knee was excised down to the fascia. The hypersensitivity of the fat pad disappeared in the region of the scar, and the fat tissues did not recur. This

6. Kling, David H.: Treatment of Myositis, Arthritis and Disturbances of the Peripheral Circulation with Histamine by Cataphoresis, Arch. Surg. 29:138-148 (July) 1934; Histamine Therapy of Rheumatic Affections and Disturbances of the Peripheral Circulation, Ann. Surg. 99:568-576, 1934; Histamine Iontophoresis in Rheumatic and Peripheral Circulatory Disturbances, Arch. Phys. Therapy 16:466-473, 1935.

result remained permanent up till now for a period of one and a half years' duration (case 1, fig. 1). This result was not duplicated by any of the other modalities. Usual physical therapy measures appeared to be the least effective, while with histamine cataphoresis there was frequently a decrease of hypersensitivity immediately after treatment. The second best result seemed to be in the 4 cases in which there was a reaction to thyroid preparations. However, the reaction fell short of expectations in view of the beneficial results with thyroid preparations reported in Dercum's disease. The excision of the painful fat, which has given such a brilliant result in 1 case, has a drawback of leaving a scar and for this reason cannot be advised as a general procedure.

COMMENT

The nosologic features and the pathologic process of juxta-articular adiposis dolorosa based on a study of 112 cases is presented. From the study it appears that hypersensitive fat pads around the joints prevail in obese multiparas past middle age. The subjective symptoms consist of pain, weakness and acroparesthesia in the extremities. The objective findings point most frequently to a slight or moderate degree of osteoarthritis. The changes in the bony structures, however, were not of such a type necessarily to produce the symptoms. The most frequent roentgenographic findings, the formation of spurs at the articular surfaces, was found in a high percentage of controls of the same age group, who were without symptoms. About 50 per cent had varicose veins, and depressed arches, a moderate or marked degree of hypertension and obstipation were found in a considerable percentage.

In the history of the preceding operations during adult life, castration takes first place, followed by appendectomy and cholecystectomy. Oral foci of infection were not found in excess of what would be expected in persons in the age groups reported on in this series. The majority of the patients showed symptoms of hypofunction of the ovaries and the thyroid gland, and few showed evidence of gross disturbance of the pituitary gland. The endocrine disturbances were more characteristic of chronic exhaustion than of infection or congenital abnormality. The most conspicuous laboratory findings were hypercholesteremia, which was interpreted to be due at least partly to a dysfunction of the thyroid gland. The histologic examination of the hypersensitive fat has, with the methods employed, not revealed any conclusive abnormality.

RELATION OF JUXTA-ARTICULAR ADIPOSIS DOLOROSA TO DERCUM'S DISEASE

Juxta-articular adiposis dolorosa presents the initial and intermediate stages which in rare instances lead to a generalized hypersensitivity of

the fat tissues. In 8 per cent of this series only the fat tissues at the inner side of one knee were hypersensitive, while in 2.7 per cent knees, elbows and thighs appear hypersensitive. With the spreading of the hypersensitivity, the patients showed the physical and mental characteristics of Dercum's disease, namely, debility and lassitude.

The course of Dercum's disease can therefore be mapped out as follows:

The initial stage appears to develop as a single uniarticular hypersensitivity of subcutaneous masses of fat of one knee, the location being mostly the inner side of one knee joint; next the other knee is involved and successively other joints in the lower and upper extremities. Finally, the condition spreads from the extremities to the torso, especially the abdomen and the lateral sides of the chest, the masses of hypersensitive fat on the chest hanging down in large folds.

The endocrine disturbances showed the intermediate stages of those described in Dercum's disease. The hypofunction of the ovaries and of the thyroid and the pituitary gland appears in the majority of cases to be due to exhaustion of the glands of internal secretion rather than to a gross pathologic process. This is also supported by the autopsy observations in cases of Dercum's disease. The thyroid was found to be small and fibrous, with sclerosis, or moderately enlarged with an adenoma. The pituitary gland showed chronic inflammation and sclerotic changes, and in the gonads atrophy and fibrosis were noted.

On the basis of autopsy, observations and clinical signs, Falta⁷ rejected the etiology of pluriglandular involvement and insufficiency of different types of lipomatosis which was advanced by Lyon.⁸ Falta regarded as the main etiologic factor of Dercum's disease a trophoneurosis due to a dysfunction of the thyroid gland which is related to myxedema.

However, in a smaller number of cases the condition develops on the basis of congenital or acquired diseases of one or more endocrine glands as illustrated in the preceding case history of juxta-articular adiposis dolorosa in a young boy and in cases 6 and 7.

THE RELATION OF JUXTA-ARTICULAR ADIPOSIS DOLOROSA TO OSTEO-ARTHRITIS

The second disease entity which has close relation to juxta-adiposis dolorosa is osteo-arthritis. As was pointed out, pain or disability in the

7. Falta, Wilhelm: *Erkrankungen der Blutdrüsen*, Berlin, Julius Springer, 1913, p. 477.

8. Lyon, I. P.: *Adiposis and Lipomatosis*, *Arch. Int. Med.* 6:28-120 (July) 1910.

joints was the complaint made by each patient in this series. Only 1 patient had infectious arthritis. The others presented symptoms which were usually classified under osteo-arthritis. Judging by the objective clinical and the roentgenographic picture, the changes in the articular surfaces of the joints were only slight or moderate. In 25 per cent of the cases the roentgenograms of the knee joints were normal, and in 57 per cent spurs of the articular surfaces were noted. These data do not exceed greatly the accidental findings in a group of patients, without symptoms, who belong to a similar age group.

The changes in the articular surfaces have been found frequently to be *minimal*, even in cases in which the condition is very advanced; therefore, it is justified to assume that the osseous changes are the sequel of soft tissue changes, one of which is presented by juxta-articular adiposis dolorosa.

This is supported by the findings in 11 per cent of the roentgenograms of changes in the soft tissues, consisting of calcification of quadriceps tendon, of hypertrophy of the infrapatellar fat pad and synovial tissue and of periostitis, especially of the anterior aspect of the patella. The frequency of the incidence of obesity, hypertension and arthritis of the knee in women of the climacteric age was emphasized by Gram.⁹ While both obesity and hypertension are common around the menopause, he found hypertension and arthritis without obesity in only 4 of 149 patients. On the other hand, obesity and arthritis without hypertension occurred in 16 patients. Obesity, therefore, outranks hypertension by far as a factor in the development of osteo-arthritis. The mechanism by which adiposis dolorosa can produce osteo-arthritis appears to consist of a number of factors.

Circulatory Disturbance.—By diverting the blood supply from the deep structures of the joints (capsule and periosteum), the increased fat masses may produce an insufficient circulation. The pressure on the deep veins obstructs the flow of blood and favors development of varicose veins. These in turn increase the stagnation of the blood. According to Wollenberg, Pemberton and others, circulatory disturbances are responsible for the development of osteo-arthritis.

Mechanical Factors.—The pressure of the increased fat masses on the capsule and periosteum and of the hypertrophic infrapatellar fat pads on the articular surfaces will tend to irritate the joint structures and interfere with the normal motion and thus cause pathologic changes. This is illustrated in figure 2 (case 2), which shows the patella pressed

9. Gram, C. A.: Symptom Triad of the Postclimacteric Period (Adipositas Dolorosa, Arthritis Genu, Hypertensio Arteriolis), *Acta med. Scandinav.* 73: 139-207, 1930.

toward the articular surfaces by the cufflike masses of fat. The anterior surfaces of the patella shows periostitis; the insertion of the infrapatellar tendon is calcified.

Functional Disturbances.—Flexion of the joint is most likely to cause pressure on the hypersensitive masses of fat. This in turn causes pain and therefore will be avoided. Interference with the normal function of the joint is the end-result.

REPORT OF CASES

CASE 1 (fig. 1).—A Jewish woman aged 54 complained of pain and stiffness in the knee joints, legs and arms and needle-like pains in the fingers of six years' duration. Her previous complaints consisted of symptoms of dizziness, headaches and cold extremities. Her bowel movements were regular. The menopause occurred at the age of 44. She had sixteen pregnancies. A cystocele and lacerations of the cervix were observed. She suffered from hemorrhoids, pruritus and eczema.

She weighed 185 pounds (83.9 Kg.) and was 57 inches (144.7 cm.) tall. Obesity was especially prominent over the buttocks, thighs and abdomen. The extremities were short. The hair was scanty under the axilla and on the mons veneris. There was a marked growth of a mustache, and the features were coarse. The lower teeth were extracted, and the patient used an upper plate. The veins were moderately varicose. The blood pressure was 130 systolic and 90 diastolic. The lungs, chest and heart were normal, as were the pupillary reflexes and ocular fundi.

The urine contained traces of albumin and epithelial cells from the bladder and vagina. The Wassermann reaction was negative, and the basal metabolic rate, minus 1. The cholesterol content was 362 mg. per hundred cubic centimeters; the calcium content, 10 mg. and creatine content, 4.3 mg.

Heberden nodes were present over the second phalangeal joints. There was no fluctuation or limitation of motion in the other joints. The masses of fat over the inner aspect of the knee joint and of the tibia were hard and sensitive to touch. Also the fat over the inner sides of the elbows and the dorsa of the arms was hypersensitive. A roentgenogram of the right knee joint was normal. A roentgenogram of the spine showed bridging at the third, fourth and fifth cervical vertebrae.

The patient was given a reducing diet of 800 calories and 3 grains of desiccated thyroid daily. In the course of two years, she received intravenous injections of typhoid, ultraviolet therapy, histamine cataphoresis and injections into the varicose veins without reduction of hypersensitivity of the fat pads. In March 1934 the fat on the inner side of the left knee was excised up to the fascia. The wound healed without complications. Histologic examination of the fat did not show any abnormality. The hypersensitivity disappeared in the region of the scar (fig. 1) and did not recur for the period of one and one-half years.

The diagnosis was multiple juxta-articular adiposis dolorosa with evidence of hypo-ovarian and hypothyroid obesity. The roentgenogram of the knee joint was normal. This is the only case in which permanent cure was achieved by excision of the hypersensitive fat at the left knee joint. One and a half years of thyroid medication did not have any effect on the other juxta-articular hyper-

sensitive masses of fat. On the contrary, the hypersensitivity progressed to the masses of fat at the lateral side of the chest, the abdomen and the back, increasing muscular weakness and mental instability. The patient now offers a full-blown picture of Dercum's disease.

CASE 2 (fig. 2).—A Jewish woman aged 45 complained of pain in the shoulders and chest. The pain in the legs was of fourteen years' duration. She had typhoid at the age of 13, and one year before the present trouble varicose veins had been obliterated by injections. Tonsillectomy was performed at the age of 28. The patient suffered from arthritis of the knees fourteen years before the present illness and spent four weeks in a plaster of paris cast. She had four children, and her menstruation was regular, the periods being of four days' duration. She was 5 feet and 4 inches (162.5 cm.) in height and weighed 270 pounds (122.5 Kg.).

Examination showed obesity, especially at the buttocks, abdomen and inner sides of the knees. Some individual knots of fat were present in these places. Over the knee joints, the fat formed cuffs, and the inner sides of the knees were tender to touch. The teeth showed pyorrhea. The blood pressure was 140 sys-

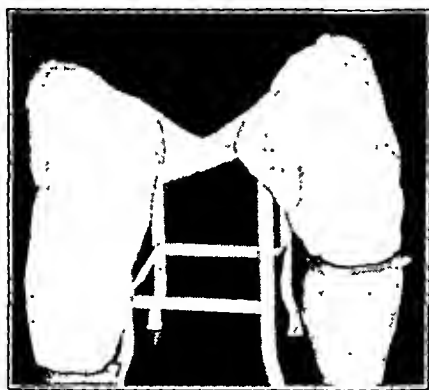


Fig. 1 (case 1).—Advanced juxta-articular adiposis dolorosa (transitional stage of generalized adiposis dolorosa). Bulging masses of fat are present over the inner side of the right knee. On the left knee there is a scar 3 inches long from excision of fat. Note the depression in the region of the scar.

tolic and 100 diastolic. The heart and chest appeared to be normal. There was tenderness over the shoulder and cervical portion of the spine. The urine was normal, and the sedimentation rate was 17 mm. per hour. The patient appeared to be of average intelligence.

On roentgen examination the spine was found to have small spurs at the upper and lower margins of the dorsal and lumbar vertebrae. The shoulders were normal, and the bone structure of the knees (fig. 2) was laazy. There was an enormous amount of fat over the joint line, forming folds which extended about 2 inches (5 cm.) below the head of the tibia. The patella was pressed toward the femur. There was periostitis over the anterior aspect at the insertion of the infrapatellar tendon.

A reducing diet and Crowe's streptococcus vaccine were given, with no effect on the hypersensitivity. This case of multiple juxta-articular adiposis dolorosa (fig. 2) illustrates the pathologic changes produced by the hypersensitive masses of fat over the knee joints.

CASE 3 (fig. 3).—A Jewish woman 58 years of age, measuring 5 feet and 3 inches (160 cm), weighing 225 pounds (102 Kg.), complained of pain in the legs of several years' duration, which was especially severe on walking. She had previously suffered from bronchitis and constipation. The menopause took place at 48. She had seven children.

On examination (fig. 3) it was found that she was obese, especially in the lower half of the body. The arches were depressed, and the fat pads at the inner sides of the knees were hypersensitive. Below the knees a constriction was seen which corresponded to the pressure of garters. The fat formed folds over the ankles. The fat over the upper extremities and the chest was not increased and had normal sensitivity.



Fig. 2 (case 2).—Lateral roentgenogram showing juxta-articular adiposis dolorosa of both knees. Enormous cufflike masses of fat are present over the knee joint. Note the approximation of the patella to the femur and calcified periostitis over the lower and anterior part of the patella at the insertion of the infrapatellar tendon.

Injections of an ovarian preparation were given with no result. The diagnosis was juxta-articular adiposis dolorosa at the inner sides of the knees, with distribution of obesity characteristic for hypofunction of the thyroid gland and ovaries. The constriction under the knees was due to circular garters. It was frequently encountered in these cases and may be a contributing factor to the prevalence and early onset of the condition around the knees.

CASE 4 (fig. 4).—A Jewish woman aged 43 complained that several weeks before the present examination she noticed a swelling over the right hip, which was painful, especially on bending forward. She had influenza in 1918 and hemorrhoids and frequent colds. She had seven children. Menstruation was starting to diminish. She was 5 feet, 4 inches (162.5 cm.) tall and weighed 150 pounds (68 Kg.). She was nervous and mentally unstable. No history of venereal disease was obtained.

Examination showed her features to be coarse; the neck was small, and the thyroid was not palpable. The arches showed a slight degree of weakness. There was no general obesity, but there was a mass of fat over the right hip joint, which was tender to touch, and the inner side of each knee and that of the right elbow were tender.

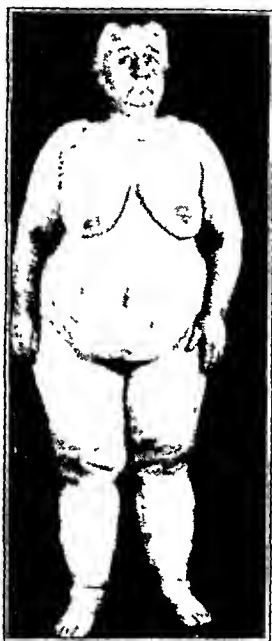


Fig 3 (case 3).—Juxta-articular adiposis dolorosa of both knee joints. Note the distribution of fat over the lower part of the body, the constriction of the garters under the knees and the bulging fat at the knees and ankles.

The sugar content of the blood was 118 mm. and the hemoglobin content, 75 per cent. The red cells numbered 4,768,000; the leukocytes, 8,500; the segmented neutrophils, 50; the nonsegmented neutrophils, 1; the lymphocytes, 44; the eosinophils, 1, and abnormal cells, 4. The basal metabolic rate was 12 plus, and the Wassermann reaction, 4 plus. The urine was normal on repeated examinations. Roentgen examination showed the ankles and shoulders to be normal, and a small spur present on the right knee.

This is a case of multiple juxta-articular adiposis dolorosa in an early stage in an otherwise not obese patient. The appearance of a hypersensitive mass over the right hip was noticed by the patient for only a few weeks. She had tertiary syphilis.

CASE 5—A Jewish woman aged 53, weighing 183½ pounds (83.2 Kg.) and measuring 57¾ inches (146.7 cm) in height, complained of a pain in the right

side of the hip and for the past three years of a pain in the lumbar region. In her youth she had suffered from headaches. Previous complaints included coughing and choking, and she had a renal condition, which was diagnosed as nephrop-tosis. She had eczema at the ears, rhinitis and scoliosis of the dorsal and the lumbar portion of the spine, which was treated by wearing a corset. Tonsil-lectomy had been performed four years before the present illness. She had had false teeth since 12 years of age. The menopause took place at 42. She had been obese since youth, and her intelligence was normal.

Examination showed obesity, especially over the buttocks, abdomen (apron-like) and thighs and the inner side of each knee, but only slight hypersensitivity. There was a marked hypersensitivity over the inner side of each knee and of each elbow. The thyroid was not palpable. There was no hair under the arm-pits, and the patient stated that she had never had hair there. There was scanty hair over the eyebrows and in the pubic region. The veins were moderately varicose. The heart and chest were normal

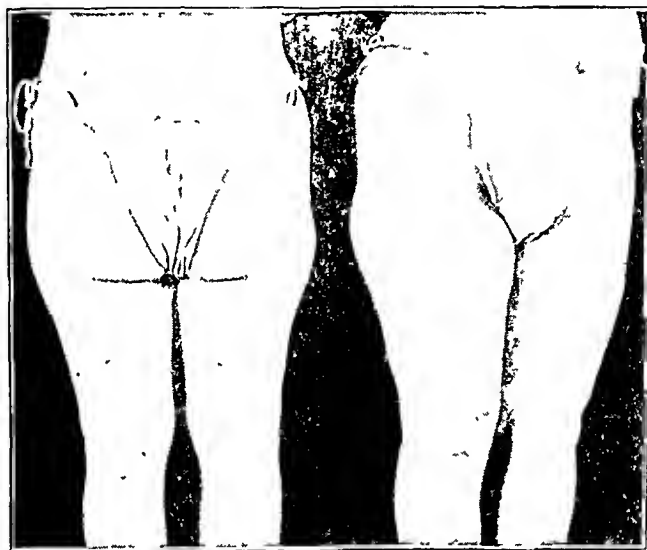


Fig. 4 (case 4).—Incipient juxta-articular adiposis dolorosa. Note the bulging masses of fat over the right hip.

Roentgen examination showed that there was scoliosis of the dorsal portion of the spine, with convexity to the right and a slight degree of coxa vara of the right femur. The urine was normal, and the Wassermann reaction was negative. The calcium content of the blood was 9.8 mg per hundred cubic centimeters and the cholesterol content, 284 mg.

The patient was put on a reducing diet, and 3 grains of thyroid daily was given for four months. The patient lost 22 pounds (10 Kg.), but the hyper-sensitivity was not influenced and was spreading.

This case of multiple juxta-articular adiposis dolorosa illustrates the failure of thyroid therapy to reduce the hypersensitive fat, although a marked reduction in general weight was noticed.

CASE 6.—A white woman aged 47 complained of pain in both arms, shoulders and knees of two years' duration. She also complained of heart burns and pain in the epigastrium. She had undergone panhysterectomy fifteen years before the

onset of the present condition, and after that there was an increase in obesity. Cholecystotomy was performed thirteen years before, and she suffered from constipation. Her oral hygiene was poor, and she had used false lower teeth for one and one-half years—two bridges—and a partial upper plate.

Examination showed her features to be coarse. She had a large nose, which she stated had grown larger since last year. The extremities, especially the hands, were large. The breasts were pendulous, and she had dry skin, although the hair was normal. She had marked knock-knees, especially of the right leg. The skin blanched after exposure to cold water for several minutes. The eyelids were puffy. There was a doughy swelling over the first phalanges of both hands. The right knee joint was 2 inches larger than the left. Fluctuation was present. A viscid turbid fluid (10 cc.) was aspirated which contained rice bodies. There were masses of fat the size of an orange on the sides of the knees, which were tender, and also there was a tenderness at the inner sides of the elbows and at the hips over the abdomen. The arms could be elevated only to 110 degrees. There was weakness in the gripping of the hands and tenderness over the third and fourth lumbar vertebrae. The blood pressure was 170 diastolic and 100 systolic. The patient had three children.

The urine showed traces of albumin and occasional hyaline casts. The blood contained 4,400,000 red cells, which under treatment increased to 5,600,000, and 80 per cent hemoglobin, which increased to 93 per cent. Under treatment the leukocytes increased from 6,600 to 9,500; the neutrophils from 35 to 50 per cent, respectively, while the lymphocytes decreased from 60 to 45 per cent, respectively.

Roentgen examination showed lipping and spurs at the articular surface of the right tibia and femur and a large sella turcica. The floor was smooth, but the posterior clinoid processes appear to be irregular. The right shoulder showed a spur at the acromioclavicular joint.

After aspiration of the fluid from the right knee, there was no recurrence of the fluid. Mild fever therapy in an infra-red cabinet and 3 grains of desiccated thyroid were given daily for a period of one and a half months. The patient lost 17 pounds (7.7 Kg.), and palpitation of the heart developed. The daily dose of thyroid was discontinued, and she regained 3 pounds (1.3 Kg.) in one week.

This case shows a transition of the juxta-articular adiposis dolorosa to generalized adiposis dolorosa. Clinical and roentgen tests showed evidence of pituitary disease and possibly the beginning of acromegaly, with physical debility and mental dulness. The patient was one of the two patients in this series who had effusion in the knee joint.

CASE 7.—A Jewish woman aged 48 complained of pain radiating from the neck to the right arm and shoulder and of stiffness of the right knee, which was especially noticeable after sitting. She also complained of frontal headaches and numbness in the fingers.

She had had a fibroid tumor of the uterus, for which she received irradiation four years before the onset of the present illness. Hemorrhages had occasionally been present in the uterus, which was treated with injections of theelin for eight months. She had eight children, and was 4 feet and 9 inches (144.7 cm.) tall and weighed 172 pounds (78 Kg.).

Examination showed scanty eyebrows and a small neck; the thyroid was not palpable. The feet and hands were small, and there were masses of fat around the abdomen and thighs. The inner sides of the knees and of the elbows were

hypersensitive. The blood pressure was 160 systolic and 84 diastolic. The lungs and heart appeared to be normal. The tonsils appeared to be chronically inflamed. The patient was dull intellectually and emotionally unstable.

On laboratory examination the hemoglobin content was found to be 82 per cent. The leukocytes numbered 8,600. The calcium content of the blood was 10.1 mg. per hundred cubic centimeters and the cholesterol content, 301 mg. The basal metabolic rate was minus 14. A roentgenogram showed the cervical portion of the spine to be normal and the sella turcica very small.

Biopsy was done of a strip of skin and subcutaneous fat of the inner side of the left knee, which was grossly and histologically normal. After the biopsy there was profuse uterine bleeding for ten days. One and a half grains of desiccated thyroid was given, which was discontinued on account of dizziness.

The diagnosis was multiple juxta-articular adiposis dolorosa in a patient suffering from the menopause syndrome. Dysfunction of the ovaries and of the thyroid gland, with a gross pathologic process of the pituitary gland, was also suggested by the small sella turcica.

CASE 8.—A Jewish woman aged 62, weighing 182 pounds (82.6 Kg.) and measuring $58\frac{3}{4}$ inches in height (149.2 cm.), complained that for the past two years she had had a cramplike pain in the left leg with dizziness, and for the past several months there was pain in the right knee. The patient also noticed a tenderness at the inner side of the right knee. The blood pressure was 230 systolic and 120 diastolic.

The patient had neuritis eleven years before the present illness; herniotomy and hysterectomy for a fibroid tumor of the uterus had been performed five years before and tonsillectomy three years before; the patient also had glaucoma simplex of the right eye.

On examination the obesity was found to be especially prominent over the abdomen, buttocks and thighs. The pupillary reflexes were normal, and the thyroid gland was not enlarged. The lungs were normal, and there was an enlargement of the heart to the left. The second aortic sounds were accentuated. The right knee joint was swollen and fluctuating. There was marked tenderness of the inner side of each knee and over the quadriceps tendon. The veins were slightly varicose. The motion of the knee was normal. A roentgenogram showed a small spur at the medial side of the articular surface of the tibia and the femur. The right hip joint was not changed, with the exception of osteoporosis of the head of the femur, which appeared in some places in the shape of round areas of decalcification. This was perhaps due to cystlike mucinous degeneration. The ocular fundi and visual fields were normal.

The urine showed traces of albumin, some pus and blood and epithelial cells of the bladder and vagina. The basal metabolic rate was plus 7. The cholesterol content of the blood was 262 mg. per hundred cubic centimeters, and the sugar content, 114 mg.

Biopsy of a strip of skin and fat 1 inch long at the inner side of the knee showed the corium to consist of coarse hyaline fibers. A large normal nerve trunk was seen. The fat was normal, with the exception of the increase in interlobular and collagenous fibers.

Twenty cubic centimeters of straw-colored viscid fluid containing fibrinous threads was aspirated. There were 400 cells per hundred cubic centimeters, and cultures in Rosenow's medium were negative. After aspiration, eighteen short wave diathermia treatments and finally six histamine cataphoreses were given. The fluid did not recur, and the tenderness over the quadriceps tendon disappeared.

The patient took 3 and 2 grains of desiccated thyroid (2.7 Kg.), respectively, for three months and lost 6 pounds. There was no effect on the tenderness over the fat masses.

A diagnosis of bilateral juxta-articular adiposis dolorosa of the knee joints with effusion in the right knee joint was made. There was a history of profuse menstruation. Hypertension and dysfunction of the thyroid and of the ovaries were noted. Although the symptoms referable to the joints were of three years' duration, the roentgenogram showed no marked changes, and the treatment promptly relieved the effusion and swelling of the joint proper. However, neither physical therapy nor thyroid medication had any effect on the tenderness of the masses of fat at the inner side of the knee.

CASE 9.—A Jewish woman aged 38, measuring 5 feet (152.4 cm.) in height and weighing 104 pounds (47.2 Kg.), complained of neuralgia on the right side for one year, with pain in the elbows and the finger joints of the right hand. Her hands and feet were stiff in the morning, and she suffered from headaches.

Her previous diseases included inflammatory rheumatism at the age of 13, chorea for three years, and vomiting for eight weeks at the age of 24. She had had extreme protrusion of the eyes and weakness of the heart. Exophthalmic goiter due to a substernal goiter was diagnosed, and ligation of the vessels of the thyroid was performed. Two years later a diagnosis was made of ulcer of the stomach, and the patient was put on a strict diet. An abscess of the pelvis was drained through the vagina, and three years before the present illness hemorrhoidectomy was performed. She suffered from chronic constipation. Her menstruation, which was profuse, lasted from seven to eight days, with an interval of fourteen days between periods. There was no pregnancy.

The family history showed that the patient's mother had scoliosis and myocarditis and an uncle had infectious polyarthritis.

On examination the patient appeared to be markedly nervous. The lungs were normal, and the heart sounds were muffled, but there was no evidence of valvular disease. The eyelids were puffy; there were an abundance of hair and a moist skin. The fat increased around the abdomen and buttocks. The blood pressure was 90 diastolic and 85 systolic. Configuration and motion of the joint were normal, and the hands and feet were cyanotic, cool and clammy. There was a contraction of the anterior metatarsal arches. The fat pad at the inner side of the left knee was tender. The urine was normal, and the blood sedimentation rate, 4 mm.

Correction of posture and change in habits relieved the constipation. The vasocirculatory and joint symptoms were treated for seven months by physical therapy and the administration of ovarian preparations, an estrogenic preparation and a follicle-stimulating principle in conjunction with $1\frac{1}{2}$ grains of thyroid daily. One course of injections of chaulmoogra oil was given. Only temporary relief was derived from all these measures. The menstruation was not influenced, nor was any appreciable rise in the blood pressure noticed. During this time the patient had several attacks of swelling and effusion of the knee of one or two days' duration. One of these attacks followed alcoholic abuse. She claimed that she had a retention of the urine for a day simultaneously with the attack.

The diagnosis was juxta-articular adiposis dolorosa of the left knee joint in a patient showing marked dysfunction of the thyroid gland and ovaries with symptoms of a transition of hyperthyroidism associated with exophthalmic goiter into hypothyroidism after thyroidectomy was performed. Deficiency of the peripheral

circulation, transitory edema, effusion into the joint, retention of urine and marked hypotension seem to indicate incipient myxedema. The juxta-adiposis dolorosa is at present confined to one knee.

CASE 10.—A woman aged 43 complained of a pain in the right arm and in the back, of two years' duration. Previously there was a pain also in the left side. She was 59½ inches (151 cm.) tall and weighed 157 pounds (71.2 Kg.). Surgical menopause took place at 35. She had two children.

Thirteen years before the present complaint she had influenza and eleven years before, tuberculosis of the lung, which was treated for six months in a sanatorium. One son died of tuberculosis. Tonsillectomy was performed fifteen years before and hysterectomy was done at the age of 35. One year before this consultation she was treated for hot flushes with injections of theelin. Two years before a tumor was removed from under the knee and left shoulder (lipoma?). The gallbladder was drained six years before, and hemorrhoidectomy was performed one year before. The patient suffered from constipation.

Examination showed the patient to be normally developed, with no enlargement of the thyroid. She also had kyphosis of the dorsal portion of the spine and cyanosis of the face and extremities. The heart appeared to be normal, as did the electrocardiogram. Percussion revealed dullness over the apexes, and there were small hard axillary and supraclavicular glands. The fingers showed Heberden nodes. There was no disfiguration of the right shoulder, but motion was limited to 120 degrees of elevation. The right pupil was larger than the left, though both reacted promptly to light and in accommodation.

Roentgenographic examination of the chest showed increased hilus and peribronchial thickening and infiltration of the infraclavicular region, with numerous small calcifications in the lung. A roentgenogram of the kidneys showed a calcified spot at the upper pole, which was movable with the right kidney and was interpreted as a calcification in the right adrenal gland. A roentgenogram of the shoulder was normal and one of the dorsal portion of the spine showed spur formation.

Laboratory examinations showed the urine to contain albumin and sometimes pus cells. The sedimentation rate of the blood was 14 mm. The basal metabolic rate was minus 2; the calcium content of the blood, 9.2 mg. per hundred cubic centimeters; the cholesterol content, 220 mg. and the nonprotein nitrogen, 22 mg. The tuberculin tests were positive with tuberculin in dilutions up to 1:1,000,000.

Biopsy of a strip of skin and fat from the inner side of the right knee did not reveal any abnormality on histologic examination.

The patient was given one injection of tuberculin weekly for eight weeks, and the pain in the right arm subsided for five months. After recurrence, treatment was continued. She received 1½ grains of thyroid daily for a month and lost 6 pounds (2.7 Kg.). No influence on the tenderness of the fat pads was noticed. The patient was transferred to a relief agency.

A diagnosis of multiple juxta-articular adiposis dolorosa was made. The climacterium was induced surgically. The history and the roentgenogram showed evidence of fibrous tuberculosis of the lungs, with a pronounced tendency to calcification. Calcification of the right adrenal gland was also visualized in the roentgenogram. The administration of thyroid had no effect on the hypersensitivity of the fat.

CASE 11.—A white woman aged 60, measuring 5 feet and 6 inches (167.6 cm.) in height and weighing 180 pounds (81.6 Kg.), complained of pain in the knees for two months. Six years before the present complaint she had thrombophlebitis

of the right leg; cholecystectomy was performed one year later. She had received roentgen irradiation for uterine hemorrhages, and since then menstruation had ceased. Her bowel movements were regular. She had four children. Her teeth were extracted.

Examination showed general obesity, varicose veins and depressed arches. The infrapatellar fat pads were increased in the knee joints, and the masses of fat at the inner sides of the knees were hypersensitive. A roentgenogram made with inflation of air showed masses of fat pressing cufflike around the knee joint, evidently pushing the patella toward the femur. The internal fat pads were markedly increased. The patient received histamine cataphoresis with indefinite effect on the hypersensitive fat.

A diagnosis of juxta-articular adiposis dolorosa at the inner sides of the knee joints was made. The hypertrophic fat pads within the joints in addition to the subcutaneous fat masses around the joints were visualized roentgenographically with inflation of air. No effect of histamine cataphoresis was noticed on the hypersensitivity of the fat.

CASE 12.—A white woman aged 58 complained of swelling and stiffness of the right knee and pain of the left arm. She suffered from hot flushes, dizziness, palpitation and constipation. Surgical menopause took place at 41. She had four children. Hysterectomy and appendectomy were performed at the age of 41.

Examination showed the patient to be nervous. No general obesity was noted. The blood pressure was 210 systolic and 110 diastolic. The heart was enlarged, and there were varicose veins. The knee joints, especially the right, showed hypersensitive masses of fat at the inner and the lateral sides of the ankle joints.

A roentgenogram of the right knee showed only calcification of the insertion of the quadriceps tendon at the patella. The urine was normal, and the Wassermann reaction was negative.

Injections of iodine and ovarian preparations were given, and the pain in the right arm and right knee decreased. There was no effect on the hypersensitivity. For this reason, a series of roentgen treatments was given, after which the sensitivity disappeared over the inner side of the knee. Procaine hydrochloride and alcohol were injected into the sensitive masses of fat at the inner sides of the ankles, and the tenderness disappeared. However, the follow-up period was short, and the duration of the therapeutic effect is uncertain.

A diagnosis of juxta-articular adiposis at the knees and ankles was made in association with a climacterium induced surgically. There was no obesity but marked hypertension. Roentgen treatment relieved the hypersensitivity at the inner sides of the knees. Injections of procaine hydrochloride had a good effect on the hypersensitive fat of the ankles.

CASE 13.—A Jewish woman aged 52 complained of pain in the feet, knees and right shoulder of three years' duration. For three months she noticed a swelling of the inner sides of the knees. The menopause was starting. The patient had five children. Her intelligence had decreased.

Examination showed a pale small neck, obesity, which was especially pronounced at the abdomen, and dermatographism. There were no previous diseases or operations. The patient had used false teeth for three years. She had enlarged tonsils and varicose veins. At the inner sides of the knees there were tender masses of fat of the size of a small apple, which were more indurated and less movable than the skin at the other side. On the inner sides of the elbows tender masses of fat the size of a walnut were present.

Baking and massage increased the pain. Injections of iodine were given.

A diagnosis of juxta-articular adiposis dolorosa in the knees and elbows was made. The tender masses of fat were increased and formed larger and smaller nodes. The patient noticed the enlargement of the masses.

CASE 14.—A Jewish woman aged 53 complained of pain in the feet and legs for two years. Examination showed weak feet and varicose veins. She had used false teeth for ten years. The menopause took place at the age of 43. She had seven children. The sedimentation rate was 13 mm.

A roentgenogram of the region of the left knee showed a spur of the tibia and the femur. The patella was pressed toward the femur and showed a separate fragment (broken spur at the upper pole).

Baking and massage increased the pain. Arch supports were worn, and injections of an ovarian preparation were given. The pain and the tenderness decreased for several months.

A diagnosis of multiple juxta-articular adiposis dolorosa was made. Temporary improvement was noted after the ovarian therapy.

CASE 15.—A Jewish woman aged 44 complained of a pain in the left knee of three weeks' duration. She was still menstruating and was the mother of eight children. Her bowel movements were regular.

Examination showed general obesity. The blood pressure was 150 systolic and 85 diastolic. She had small feet and hands, which were cyanotic and felt numb. She had a small neck. The thyroid gland was not palpable. The arches were depressed, and the veins were moderately varicose. Masses of fat the size of a walnut protruded at the inner side of both knees and were sensitive to touch. The infrapatellar fat pads were markedly large but not sensitive. The painless right knee showed more marked grating on motion than the left knee. There was limitation of flexion in the left knee to about 50 degrees on account of pain.

A roentgenogram of the left knee showed only a slight irregularity of the patella. The fat was enlarged. Histamine cataphoresis was given six times, and the range of motion increased to 90 degrees of flexion. The hypersensitivity of the fat pad diminished, but temporarily.

The diagnosis was juxta-articular adiposis dolorosa of the knees, with decrease in flexion on account of pain. Histamine cataphoresis diminished hypersensitivity and increased the range of motion.

SUMMARY

A study of 112 cases of hypersensitive masses of fat at the joints is presented.

The term juxta-articular adiposis dolorosa is suggested for this condition, to express the location and the relation to generalized adiposis dolorosa.

The condition prevails in obese multiparas past middle age.

The condition is frequently associated with hypertension, varicose veins and depressed arches.

Subjective symptoms consist of pain, weakness, stiffness in the joints, acroparesthesia and circulatory disturbance in the extremities.

The inner sides of the knees were involved in 95 per cent of the cases. In 8 per cent only one knee joint was hypersensitive. In all others the condition was bilateral.

Clinical and laboratory examination revealed in about 60 per cent of the cases slight or moderate osteo-arthritis; in 11 per cent, soft tissue changes, such as hypertrophy of the infrapatellar fat pads, and periostitis, especially over the patella or calcification of the insertions of quadriceps tendon, were noted. Joint effusions were present in 2.6 per cent.

Among diseases and operations in the adult life of patients, castration, appendectomy and cholecystectomy were conspicuous.

Oral foci of infection were not found in excess of what would be expected in patients of the age groups in this series.

Hypofunction of the ovaries and of the thyroid and the pituitary gland was frequently found. In the majority of cases glandular disturbances were characteristic of chronic exhaustion rather than of acquired or congenital gross pathologic processes.

The basal metabolic rate was lower in only 33 per cent. In 87 per cent a definite hypercholesteremia was found, which appeared to be partly due to dysfunction of the thyroid.

Biopsies of fat pads did not reveal definite pathologic processes.

Juxta-articular adiposis dolorosa is regarded as the initial and intermediate stage of generalized adiposis dolorosa.

Juxta-articular adiposis dolorosa is recognized as one of the soft tissue changes which leads to the development of osteo-arthritis by interference with the blood supply, by pressure and irritation of the structures of the joint and by interference with the function of the joint.

Permanent disappearance of hypersensitivity and reduction of the fat followed excision in 1 case. All other therapeutic measures, including the administration of thyroid and ovarian preparations, histamine cataphoresis and roentgen therapy, had only a partial and frequently transitory effect on the hypersensitivity of the fat pads.

Dr. Cyrill B. Corville, of Los Angeles, supplied special stains of the biopsy sections, and Dr. David Saschin, of New York, furnished some of the follow-up data.

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TREATMENT OF BRAIN ABSCESS ASSOCIATED WITH EXTRACAPSULAR NECROSIS AND SUPPURATION

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The experience gained in the treatment of two patients with abscess of the brain associated with extracapsular necrosis and suppuration forms the basis of this paper. These are the only patients with this type of abscess whom I have ever seen. Both were operated on, and both recovered. In presenting this subject with the report of the cases, I hope that the information obtained from the observations made will be of help to others in dealing with similar cases.

In reviewing the literature one does not find reports of many cases of nonoperative abscess of the brain in which definite pericapsular or extracapsular involvement in the nature of necrosis and suppuration was present. This may be due to the fact that autopsy was not performed or that the condition found at autopsy was not completely described. Probably Macewen¹ and Eagleton² have given more attention than most writers to the detailed description of the individual cases observed by them. In one instance Macewen (case 28) stated that "it was evident that there was a considerable zone of purulent inflammation surrounding the abscess cavity," but this was only an assumption, as the area was not completely inspected and observed. The patient recovered. In another instance (case 30) Macewen removed at autopsy a rather large capsule which was completely floating in pus. The abscess ruptured into the ventricle. In other instances he spoke of the abscess cavity's being "surrounded by a slightly reddish-yellow zone," or "red softening of the brain."

Eagleton reported a case (case 9) in which the pathologic process was similar to that in the two cases here reported. He also gave his reasons for the formation of secondary abscesses as follows: "encephalitis induced in surrounding tissue by the trauma of exploration or evacuation" and "encephalitis by direct extension from the primary

Read before the Section of Neurology and Psychiatry of the New York Academy of Medicine, April 9, 1935, and before Westchester Surgical Society, April 23, 1935.

1. Macewen, William: *Pyogenic Infective Diseases of the Brain and Spinal Cord*, Glasgow, J. Maclehose & Sons, 1893.

2. Eagleton, W. P.: *Brain Abscess: Its Surgical Pathology and Operative Technic*, New York, The Macmillan Company, 1922.

abscess, the path of infection, though frequently small, being discoverable by careful examination." In the large number of cases reviewed by him there probably were a number similar to the two reported here.

Mosher³ removed a capsule in its entirety. Bagley⁴ also reported a case in which the same procedure was carried out. Adson and Craig⁵ reported the removal of an encapsulated abscess without being aware of its nature until the mass was opened. The wound healed by primary intention without drainage. Evidently extracapsular suppuration or necrosis was not present. Cahill,⁶ in a report on his series of cases of abscess of the brain, in which the recovery rate was high, did not mention extracapsular involvement. In 1930 Coleman⁷ stated that in his experience death after operation in all of his fatal cases, with one exception, was due to septic encephalitis, and he commented on the striking contrast between the condition of the patient before operation and that after the surrounding brain had been traumatized and infected in an attempt to drain the pus. He further stated that in such an instance the whole process of reencapsulation must be repeated by the brain tissues if the patient is to survive. However, no mention was made of finding extracapsular suppurative encephalitis or necrosis coexistent with an encapsulated abscess for which operation had not previously been performed. It is not known whether he encountered this condition. Adson and Craig⁵ and Grant,⁸ in their respective reports of large series of cases, do not describe this condition. Penfield, in a personal communication to Adson and Craig, stated, in reference to the formation of the capsule, that the course of the abscess, if drainage is not established, depends on the nature and virulence of the organism, and that if an insufficient wall or capsule is not formed, spreading encephalitis with edema of the brain may quickly terminate the patient's life. It is believed that this statement was not meant to apply in any sense whatever to a well encapsulated abscess.

Were a fairly wide-open exposure, which would allow of proper inspection, made at operation for abscess of the brain and were com-

3. Mosher, H. P.: Personal communication to the author.

4. Bagley, Charles, Jr.: Brain Abscess with Pathological Observations, *Surg., Gynec. & Obst.* **38**:1-13 (Jan.) 1924.

5. Adson, A. W., and Craig, W. McK.: The Surgical Management of Brain Abscess, *Ann. Surg.* **101**:7-26, 1935.

6. Cahill, Harry P.: Twelve Cases of Cerebral and Cerebellar Abscesses Drained by the Mosher Wire Gauze Cone, *Tr. Am. Otol. Soc.* **17**:42-66, 1925.

7. Coleman, C. C.: Reduction of Mortality of Brain Abscess by Simple Methods of Treatment, *South. M. J.* **23**:484-487, 1930.

8. Grant, F. C.: The Mortality from Abscess of the Brain, *J. A. M. A.* **99**:550-556 (Aug. 13) 1932.

plete reports made of autopsies in the fatal cases, no doubt a coexisting, noncommunicating, extracapsular suppurative or necrotic process would be found in the brain substance in a number of cases. Considering the uneventful course in the two cases here presented, it is believed that recovery would take place in many such cases. Mosher stated that the possible presence of the associated extracapsular necrosis and supuration of the brain may have been responsible for some of the fatalities in cases in which his drain was used.

REPORT OF CASES

My first case has already been reported;⁹ so only a brief review of this will be made. Following the precepts of Macewen and Eagleton, a more detailed report of my second case will follow.

CASE 1.—A woman aged 45, referred to me by Dr. Foster Kennedy, was seen at the Manhattan Eye, Ear and Throat Hospital. A nasal infection developed in the last week of March 1932. On April 1 there was severe pain in the left ear. Myringotomy was performed, but the pain continued. On April 3 the patient suffered from severe headache and vomiting. Two days later rigidity of the neck developed, which became more pronounced. There was diminution of the right abdominal reflex, and a positive Kernig sign was elicited. A diagnosis of meningitis was made. Lumbar puncture showed a cloudy fluid. Antimeningococcic serum was administered. Culture of the spinal fluid was negative. Lumbar punctures were made on April 6 and 7. On April 8 the temperature dropped from 105 to 96 F. On April 9, erysipelas of the face developed, which lasted a week. Discharges from the ear and nose showed *Streptococcus haemolyticus*. The patient's general condition improved, and the meningeal symptoms cleared, although on April 10 the patient suffered from severe headache and vomiting. On April 17 to 20 neurologic examination showed slight anomia, slight flattening of the lower part of the right side of the face and diminution of the right abdominal reflex. There were slight fulness of the veins of the fundi, and a defect in the upper quadrant of the visual field. The patient's general condition improved, but the headache persisted. The temperature became less but never returned to normal. Anomia continued. Lumbar puncture showed 70 lymphocytes. The meningeal signs cleared. Some pain was felt behind the left ear, and there was a profuse discharge on two occasions. Roentgenograms showed some softening in the region of the mastoid antrum. A diagnosis of probable subdural abscess with possible abscess of the brain was made.

Mastoidectomy, performed by Dr. Ross Faulkner on April 20, revealed an eburnated mastoid, with practically no cells. Exposure of the lateral sinus gave negative results. However, soft necrotic bone was found in the roof of the aditus. The dura was exposed. It was tense and did not pulsate. No pathologic process pertaining to the subdural space was found until the basilar dura was elevated; then there was a discharge of pus. Repeated elevations of the dura were followed by the evacuation of more pus each time. This pathologic process, coupled with

9. King, Joseph E. J.: Brain Abscess: External Rupture of "Capsule" with Pericapsular Brain Necrosis, *Ann. Surg.* **101**:190-200, 1935; The Treatment of Brain Abscess by Unroofing and Temporary Herniation of Abscess Cavity with the Avoidance of Usual Drainage Methods, *Surg., Gynec. & Obst.* **39**:554-568 (Nov.) 1924.

symptoms and signs of a lesion involving the left temporosphenoid area, made one suspect and diagnose the presence of an abscess of the brain in this region with evacuation through the area of the mastoid. The leukocytic and polymorphonuclear counts on April 22, 23 and 24 were: 27,300 and 90; 22,100 and 89, and 19,600 and 80, respectively. The results of the previous neurologic examination, with the Babinski sign and ankle clonus on the right side, an increase in the tortuosity of the veins and drowsiness, were sufficient evidence to warrant the diagnosis of an abscess in the left temporosphenoid area.

Operation was performed on April 25. A small opening was made in the left temporal region, rather high up on account of the mastoid wound. A cannula directed into the temporosphenoid lobe failed to meet with the resistance offered by a capsule. Thick greenish yellow pus, however, was recovered by aspiration. A section of bone between the trephine opening and the mastoid wound, about $1\frac{1}{2}$ inches (3.8 cm.) in diameter, was removed. The dura was fixed to the cortex by electrocoagulation. The cortex was somewhat injected. There was an area of underlying softening. Removal of the cortex at this site by suction revealed necrotic brain substance and, deeper in, actual thick yellow-green pus. After removal of this material by suction, a shriveled, collapsed, thickened capsule of an abscess came into view. It was floating freely in pericapsular pus except at the base, where it was firmly attached to the basilar dura at the site of spontaneous rupture. No utilization of the capsule could be made for the purpose of drainage. It was therefore excised, leaving the immediate basilar attachment to the dura. The capsule was empty, except for a thin layer of thick, inspissated greenish pus plastered onto the inner wall of the capsule. All pericapsular necrotic brain tissue and pus were removed by suction until the brain substance seemed to have a normal appearance. The ventricle was not entered. The cortex, for a depth about $\frac{1}{2}$ inch (1.3 cm.), was not involved in the necrosis. No method of drainage to meet the requirements of this condition had ever been described; at least none was known to me. A "handkerchief" of iodoform gauze was depressed into the existing excavation in the brain, which was loosely packed or stuffed with fluffed iodoform gauze in the same way that the Mikulicz drain is introduced. Copious gauze dressing and treatment with a diluted solution of sodium hypochlorite were employed.

The iodoform gauze was gradually removed on the sixth day, accompanied by gradual herniation, which was mild. The surface of the brain substance presented the distinct appearance of fibrosis and offered resistance to pressure—a distinct contrast to the soft friable brain substance seen at the time of operation.

There was slight herniation, the surface reaching but little above the level of the skull. Lumbar puncture, performed on May 24, with removal of 15 cc. of clear fluid, diminished the size of the hernia, and its level subsided. The granulating surface was completely epithelized. The patient was discharged on the fiftieth postoperative day. The area was completely healed over on the sixty-fifth day.

On November 7, a radical operation was performed on the left antrum by Dr. Faulkner.

On April 12, 1933, a plastic operation was done on the scalp, with excision of the scar.

At present the patient is completely recovered, except that at times there is misuse of a word.

CASE 2.—L. B., a surgeon aged 55, was referred to me by Dr. Leopold Stieglitz and by the patient himself.

History (from notes by the patient).—The patient had had attacks of severe frontal pain since childhood. He was treated for a long time during childhood for exophoria and wore prisms from about 1895 to 1900. He had headaches in the morning, which increased in intensity during his attendance at medical school. This was especially noted on the left side. In 1910 the middle turbinate on the left side was removed, and the patient had severe attacks of left frontal sinusitis. The question of an external operation was then discussed, but this procedure was rejected. From 1910 to 1918 he was under treatment for sinus disease, during which time numerous punctures of the antrum, with irrigations, were done. In 1918 an intranasal operation to relieve the frontal headache was done. During this procedure the septum was resected, and the ethmoid sinuses were opened and drained. During the operation marked hemorrhagic extravasation of the conjunctiva was noted. There was increase of pain in the region of the left orbit and the left frontal area after the operation. Five days after the operation there were marked edema of the eyelids and protrusion of the bulbus oculi. The diagnosis of an extra-orbital exudate was made. A radical external operation on the frontal sinus was performed six days after the intranasal procedure. A large portion of the mesial osseous wall of the orbit was removed. The incision was closed, with a drainage tube passing down through the naso-frontal duct into the nose.

The frontal headaches were somewhat improved after the operation, but the headaches in the sphenoid area became unbearable.

In the interval between 1918 and 1928 a large number of intranasal procedures were done. Portions of the ethmoid bones were removed. On several occasions openings into the sphenoid sinuses were made as well as permanent openings into both antrums. The tonsils were also removed. In 1920 mastoidectomy was performed on the left side. The operation was complicated by pneumonia type I. Serum sickness developed, although desensitization had been carried out. In 1928 a diagnosis of "intranasal neuralgia" was made by a well known rhinologist, the neuralgia being given as the cause of the persistent pain in the left orbit and the left frontal region. The patient believed that a focus of pus existed somewhere in the left ethmoid region and that this focus was being poorly drained. He therefore importuned Dr. Stuart L. Craig to continue his examinations. These efforts were rewarded by the finding of a passage which led upward and apparently into a para-orbital cell below and to the outer side of the frontal sinus. This position of the probe was confirmed by roentgenograms. Thereafter the treatment consisted in keeping this tract open so as to allow the drainage to continue. Nevertheless, there was a persistence of continuous headaches, which were especially severe in the morning, and intense boring pain was felt in the left orbit. These symptoms suggested to the patient that there were inflammation and breaking down of the bone. In 1930 to 1931, believing that his condition would be improved in a warmer climate, he went to the southern part of California. Improvement did not follow his residence there. In fact, during this stay he had numerous attacks characterized by swelling of the lids of the left eye, especially in the region of the inner canthus. In the winter of 1932-1933 he had marked symptoms of radiculitis of the left lumbar region, with pain radiating down both legs, especially in the left. These pains lasted for about four months.

For several years the patient had been accustomed to pass an applicator into the tract in order to relieve the pains in the frontal and ethmoid regions to some extent. He had noticed that a modicum of relief followed gentle insertion of the nasal probe into this tract with slight movements of the probe. In May

1934 he stated that he was "shocked to find one day that the probe passed readily upward without interference far beyond the probable upper level of the frontal sinus." As this event was unattended by any apparent deleterious effect, and for a number of reasons, the experience was not related to his physician until July 1934.

During July and August 1934 he observed that there were "increasing weakness of the right hand, attacks of pain in the joints, excessive perspiration on exertion, two attacks of vertigo and at least three attacks of fever lasting several days."

In September 1934 he realized that intracranial intervention was necessary, his conclusion being based on the febrile attacks, the increasing weakness of his right hand and the increase of headaches and pains in the head.

On Sept. 29, 1934, a consultation was held in the patient's apartment. Drs. Stieglitz, Kennedy, Craig and Neal and I were present.

Neurologic Examination (Dr. Foster Kennedy).—"The patient's trouble was in the left frontal and temporal lobe. The diagnosis made was abscess in the left frontal region, with the extension from that implicating in some way the left temporal lobe. My reason for saying this was that he had weakness of the lower part of the right side of the face on smiling and on expressing emotions. At the same time, when sending for an ophthalmoscope, he could not remember the name of the man who had been his assistant in practice for many years. That was the first thing that made me know he had anomia. He had weakness of the right abdominal reflex as compared with the left, and weakness of the right grasping reflex as compared with the left. I could find no change in the plantar reflexes. He was perfectly well oriented and inspected his own x-ray films with knowledge, insight and self-restraint. The left fundus was a little blurred. The right was normal. There was no change in the visual fields."

Roentgenographic Examination.—Roentgenograms were made on September 27 by Dr. Dunn after the passage of probes by Dr. Neal into the left nares upward and backward, one being directed toward the sphenoid region and the other toward the ethmoid region. The films showed the probes in situ. In the lateral (fig. 1) and anteroposterior views the anterior probe was seen to pass through a perforation in the ethmoid horizontal plate for a distance of 4.5 cm. into the left frontal lobe. This position of the probe was readily seen in the lateral stereoroentgenograms.

The bone was observed to be necrotic from a point about 0.5 cm. anterior to the opening through which the probe passed, backward toward the sphenoid sinus for a distance of 2.5 cm. The remainder of the bony plate forming the superior plate or wall of the sphenoid sinus appeared to be in good condition. One could not tell exactly the size of the opening in the ethmoid bone, but it was sufficiently large to allow the passage of the probe. The lower probe passed more backward, into the region of the lower part of the sphenoid bone. There were cloudiness and an indefinite haziness in the frontal region. The antrums were fairly clear in the lateral films. In the anteroposterior view (fig. 2) the left antrum appeared to be clear, while the right was cloudy. The latter films also showed that some operative procedure had been done in the area of the left frontal sinus. The two probes likewise could be seen. The anterior probe, after passing up through the ethmoid region, curved or bent somewhat outward, its tip being approximately 2 cm. from the midline. The history of long-standing involvement of the frontal, ethmoid, and sphenoid sinuses (about seventeen years), the roentgenograms showing the probe passing through the ethmoid bone into the

left frontal lobe, the history of the ready passage of the probe without marked intracranial episode, the presence of the severe, prolonged and sustained pain in the head, the history of repeated discharge of pus from this region and Dr. Kennedy's findings led one to suspect the presence of an old, chronic abscess of the brain in the left frontal region, which had partly evacuated itself or had been evacuated through the ethmoid region into the nose.

It was decided that it would be advisable to have the patient or Dr. Neal insert a small cannula into the opening through which the probe had been passed, and if the cannula passed readily, injection of a small amount of air should be done to determine the presence, if possible, of such an old, chronic abscess. A small cannula was placed in the opening of the ethmoid region and passed upward rather easily, in a manner similar to that of the probe. Injection of air was done slowly, with a small syringe. After a few cubic centimeters of air



Fig. 1 (case 2).—Lateral roentgenogram showing a probe (A) passed through an opening in the necrotic horizontal plate of the ethmoid bone for $1\frac{7}{8}$ inches (4.7 cm.), $\frac{3}{8}$ inch (0.9 cm.) beyond the inner wall of the abscess cavity shown in figure 3. The second probe passed toward the sphenoid sinus.

had been injected, the patient stated that he could feel a little "tightness" or slight "fulness" in the left side of his head. The cannula was therefore withdrawn; the patient walked to the roentgenographic room, and stereoroentgenograms were made, both anteroposterior and lateral views. The films showed the presence of a multilocular cavity, which was assumed to be a partially collapsed abscess cavity. In the lateral view (fig. 3) the anterior cavity appeared to be almost vertical, extending upward from the perforation in the ethmoid bone for 2.5 cm., and measuring 2 cm. in its greatest diameter in the lateral direction. This air shadow was the shape of a balloon or of a small fig. Its most anterior portion was 8 mm. from the inner table of the skull. The second air shadow was ovoid or somewhat the shape of a drawn-out bird's egg, being rounded at both ends. It lay in a horizontal direction, practically at right angles to the first cavity or air

shadow. It measured 3.5 cm. horizontally and 2 cm. vertically at its greatest width. The posterior extremity of this air shadow was about twice the size of the anterior extremity; i. e., the small end was directed forward. The second air shadow was more distinct than the first. Whether this was due to the fact that more air was present in the upper horizontal air cavity or whether the wall of the lower vertical one was thicker was not known. Near the anterior pole of the second or horizontal cavity it could be seen that the lower cavity overlapped the upper one, both in the flat roentgenogram and in the stereo-roentgenogram. The overlapping of the wall of the one cavity on the other was very definite and was shown by the denser air space, measuring horizontally about 0.5 cm., and vertically about 1.2 cm. (This later proved to be the communication between the two abscess cavities.)

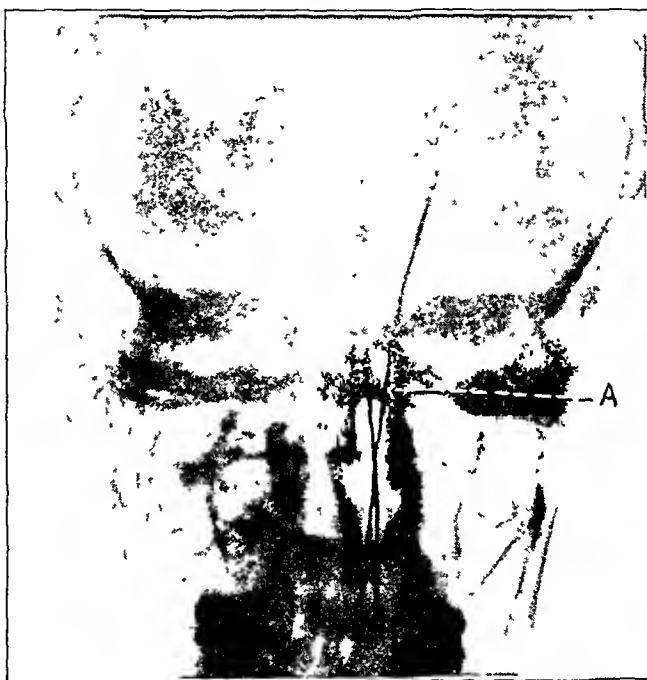


Fig. 2 (case 2).—Anteroposterior roentgenogram showing a probe passed through an opening in the ethmoid bone into the left frontal region.

In the anteroposterior view (fig. 4) two distinct air cavities were likewise shown. The horizontal, or second, cavity was seen more distinctly than the first, as was the case in the lateral view. The first, or anterior, air chamber or cavity measured 1.5 cm. transversely and overlapped the second cavity. The second air cavity was likewise somewhat balloon shaped and measured 1.5 cm. laterally and 2 cm. vertically. There was a trace of air directed downward toward the ethmoid region, where it lost itself. The two air cavities, superimposed with the prolongation of air downward toward the ethmoid region, somewhat resembled the shape of a small tennis racquet. The lower limit of the central portion of the second cavity was 6 mm. above the supra-orbital ridge, and in the lateral position it was about halfway between the inner and the outer canthus. The center of this cavity was 3.5 cm. from the midline. The pineal gland could be distinctly seen, with possibly a slight shift toward the right.

Diagnostic Opinion.—From the history, physical findings and roentgenograms, it was concluded that there was present in the left frontal lobe a multilocular, or multiple, abscess of the brain, probably of long standing. It was assumed that the abscess had at least two fairly distinct connecting cavities, the posterior one of which probably was secondary to the anterior one and probably was an extension from it.

Examination of the Blood (Sept. 27, 1934).—The hemoglobin content was 92 per cent. The white cells numbered 10,400, with 79 per cent polymorphonuclears (segmented 75 per cent, staff 3 per cent and basophil 1 per cent), 1 per cent lymphocytes and 3 per cent monocytes.



Fig. 3 (case 2).—Lateral roentgenogram after the injection of air into the abscess cavity. *A* indicates the smaller anterior cavity connected with an opening in the ethmoid bone by a fistulous tract or stalk, and *B*, the larger posterior horizontal cavity connecting with and overlapping the anterior cavity at *C*.

The patient was admitted to the Harbor Hospital for operation on Oct. 2, 1934, with a temperature of 99.4 F, a pulse rate of 80 and a respiratory rate of 20.

Operation.—From observations and measurements on the roentgenogram the anterior wall of the first or anterior abscess was located at a depth of 1 cm. from the inner table of the frontal bone. It was decided to corroborate this

information definitely by making a small trephine opening over the supra-orbital ridge at the proper position and inserting a brain cannula through a small nick in the dura. A straight vertical incision about 2.5 cm. in length was made over the left side of the forehead, perpendicular to the central portion of the eyebrow. Through this incision an opening was made in the skull just above the supra-orbital ridge, the opening being about 1 cm. in diameter. The cannula was inserted through a small incision in the dura. It was passed directly backward and, on the first puncture, at a depth of 1 cm., it met with firm resistance offered by the capsule of the abscess (fig. 5).

After the exact position of the abscess had thus been determined, it was considered advisable that the operation which was to be done by Dr. Craig should be performed first and that the operation for the abscess should follow. The small



Fig. 4 (case 2).—Anteroposterior roentgenogram showing the two cavities seen in figure 3. The lower inner anterior cavity (A) connects with the opening in the ethmoid bone by a fistulous tract or stalk (C).

nick in the dura was sealed off by electrocoagulation, and a plug of cotton was placed in the small trephine opening. This was done to block off the subdural space and prevent the spreading of infection into it. The incision was then carried down through the old scar, which resulted from the previous operation on the frontal sinus. This scar was excised, and the scalp flaps, three in number, were reflected and held with self-retaining retractors. This exposure gave adequate access to the remnants of the frontal sinus and the ethmoid and the sphenoid regions.

The operative procedure, performed or carried out by Dr. Craig, was described by him as follows:

An incision in the ethmoid region was made following the approximate line of the old scar. This incision was carried down to a probe which had been

passed into the old sinus opening. The previous operation was found to have been well completed. The orbital plate of the ethmoid had been completely removed, the ethmoid well exenterated and the sphenoid widely opened.

The diseased area consisted of necrotic bone lying against and including the basal plate of the skull, a part of which came away as a sequestrum on both sides of the opening through the dura. A posterior ethmoid cell lying in the angle between the orbit and the basal plate was found to contain infection, and a cell of the middle ethmoid, very high up, was also infected. All diseased bone was removed, and the ethmoid cells were completely eliminated. There was no necessity for interference with the sphenoid or with the antrum.

On completion of this procedure, the nasal cavity of the left side was well packed off with strips of iodoform gauze so as to prevent leakage of blood into the nasal cavity. (A postnasal plug had previously been introduced.) The trephine opening which had previously been made was then enlarged, first in a

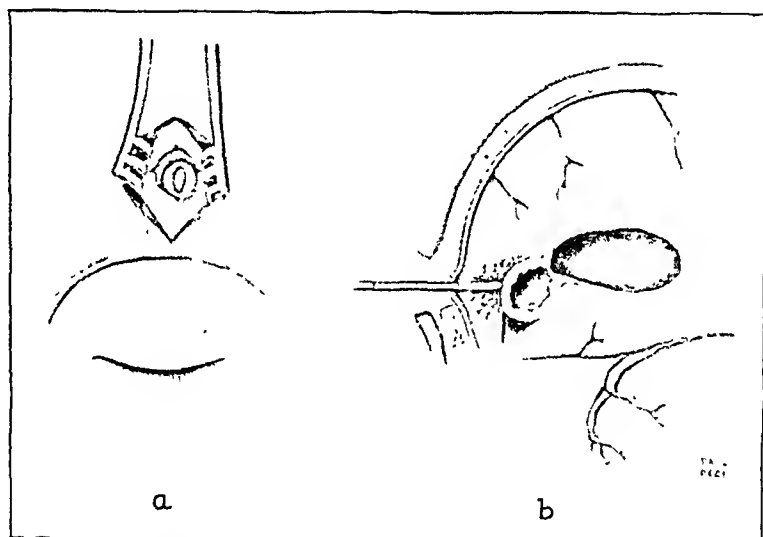


Fig. 5 (case 2).—The trephine opening made in the supra-orbital region over an old scar in the eyebrow, with a small incision in the dura, is shown in *a*. The cannula was then passed through the dural incision and through soft, extra-capsular necrotic brain substance, where it met with firm resistance against the wall of the anterior abscess at a depth of 1 cm., as shown in *b*.

circular manner to about the size of a half-dollar. The dura was fixed to the cortex near the margin of the bone with the electrocoagulation tip and was opened in a stellate fashion; the dural flaps were cut away and discarded. The dural margin was more adequately fixed to the cortex, and strips of iodoform gauze were placed around the bony and dural margins, where they became fixed in position. The cortical surface exposed was about the size of a 2 frame piece. The cortex overlying the anterior portion of the capsule of the abscess was sucked away. Owing to the fixation of the dura to the cortex, there was no tendency for the latter to fall away or droop or sag from the dura. There was no fear, therefore, of soiling or spreading the infection through the subdural and subarachnoid spaces.

At a depth of 1 cm. the anterior surface of the capsule of the abscess came into view. As it was being exposed, it was observed that the brain tissue, especially about the anterior, external and superior portions of the capsule, was necrotic, yellowish and broken down (fig. 6). Nearer the capsule there was thick yellow pus. The anterior half of the anterior capsule was removed (fig. 7). The abscess cavity contained thick yellow pus, without a foul odor. A specimen sent to the laboratory was reported to contain *Streptococcus haemolyticus*.

Adequate inspection of the cavity could then be done. As the pus was removed by suction and cotton pledgets, an opening about 1 cm. in diameter was seen at the upper posterior pole of the capsule. From the opening the same type of thick yellow pus exuded in a pulsating fashion, corresponding with the heart beat.

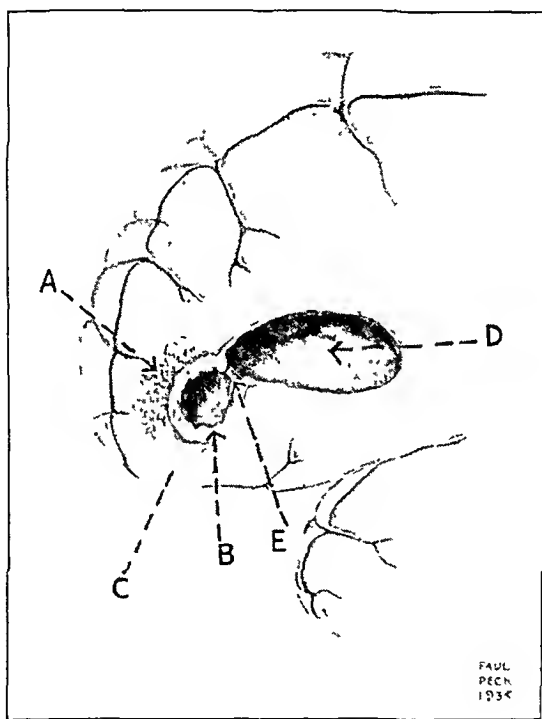


Fig. 6 (case 2).—A schematic section of the lesions, showing extracapsular necrotic and suppurative brain substance (A); the very thick wall of the smaller anterior abscess (B), with the "stalk" (C) leading downward and inward to the opening in ethmoid bone, and the posterior, and larger, abscess cavity (D), with a definite, but thinner wall which connects with the anterior cavity through an opening (E).

This opening led into a second abscess cavity, which was horizontal in position and similar to the air shadow shown in the roentgenogram. The cavity, which was partly collapsed, measured from about $\frac{5}{8}$ to $\frac{3}{4}$ inch (1.6 to 1.9 cm.) in diameter and about $1\frac{1}{4}$ to $1\frac{1}{2}$ inches (3.2 to 3.9 Gm.) in length. This capsule was much thinner than the anterior one, showing that the abscess was of more recent origin. The wall of the anterior cavity was about $\frac{1}{8}$ inch (0.3 cm.) thick, or perhaps a little thicker, while that of the posterior cavity was about 1 mm. in

thickness. The posterior cavity was therefore evidently an extension from the more ancient, anterior abscess cavity, as a result either of spontaneous rupture backward or of trauma produced by the probe.

The anterior abscess had a "stalk" or tract which led from its lower pole inward, forward and downward to the ethmoid region. It was necessary to remove bone far down toward the nasal cavity in order to uncover this tract and to determine the exact point where it perforated the base of the skull in the anterior fossa. This was found to be the horizontal plate of the ethmoid sinus, in the same position as shown on the x-ray films. Necrotic bone about the opening of this tract was removed. The lumen of the tract was just sufficient to allow the passage of an ordinary silver probe. The shape of the anterior abscess was that of an elongated balloon or an unripe fig, the capsule corresponding to the fig itself and the tract to the stem of the fig. The transverse diameter of the abscess capsule at its greatest width was about 1 inch (2.5 cm.). The wall was

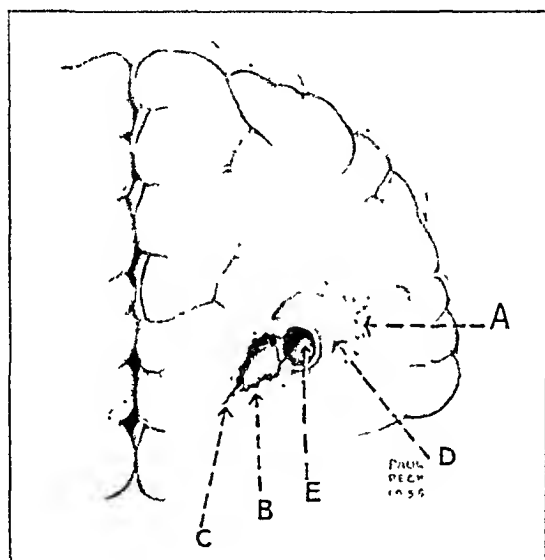


Fig. 7 (case 2).—A schematic section of the lesions, showing where the anterior half of the thick wall of the anterior abscess (B) and its stalk (C) were cut away and the opening (E) about 1 cm. in diameter between the anterior and the posterior (D) abscess cavity. A considerable amount of brain substance between the lateral cortex and the abscesses was necrotic and contained pus. No connection between this area and the cavities was detected.

rigid and did not tend to collapse. The anterior wall of the tract was removed, and the posterior half of the tract and its connecting capsule were left attached to the brain substance in order to keep the brain fixed at this point so as to prevent overherniation. The granulating inner surface of the tract was curetted gently and swabbed with phenol and then with alcohol.

The extracapsular necrotic brain tissue and pus were then removed by suction, until the brain substance presented a rather normal appearance. This sucked-out excavation in the brain led back alongside of, and external to, the second or posterior abscess cavity for a distance of about $\frac{3}{8}$ inch (0.9 cm.). The exposed lateral wall of the posterior abscess was then removed so as to lessen

the relative depth of the cavity and to afford more adequate drainage. It was expected that the remaining posterior portion of this cavity would move or herniate forward and so "catch up" with the remainder of the excavation in its forward progress.

The procedure was now completed except for the dressing. A small strip of soft iodoform gauze was loosely stuffed into the remaining portion of the posterior cavity. A "handkerchief" of iodoform gauze was then placed over the excavation in the brain and depressed so that it came in contact with the brain substance, and the opening was loosely stuffed or packed with fluffed iodoform gauze in the manner of the Mikulicz drain, except that iodoform gauze was used in place of rubber dam. The nasal and supra-orbital region were also well packed off with iodoform gauze. The flaps were replaced and loosely sutured. A copious gauze dressing wet in a dilute solution of sodium hypochlorite was applied over the entire area and held with a slightly compressing bandage, which passed over the head and the lower jaw. Both eyes and ears were covered well with petrolatum gauze and were included in the dressing. The patient withstood the operation well.

After the operation it was considered advisable to give a blood transfusion. This was done on the operating table by Dr. Eggston. The patient left the operating room in good condition.

NOTE.—In this case two distinct abscess cavities existed. The posterior one had probably existed for not more than three or four weeks, and the anterior one, probably much longer. The posterior cavity connected with the anterior one, and it in turn was connected with the nasal cavity by means of a fistulous tract or "stalk," which allowed both cavities to drain incompletely through into the nasal cavity. (One could compare the situation with a system of lakes drained by a river.) In addition, there was a considerable amount of extracapsular necrotic brain substance and thick yellow pus which did not connect with or drain into the abscess cavity. To complicate matters, the area of the extensive procedure performed by Dr. Craig was in immediate juxtaposition, and was continuous with, the area involved in the intracranial procedure. This was the first time that I have observed this to occur.

Therefore, the questions which arose were: Will the posterior portion of the posterior abscess cavity herniate forward sufficiently to obliterate it? Will the brain hernia proceed forward and project into the nasal cavity? How can one block off the nasal portion from the intracranial portion of the operative area so that proper treatment of the intracranial area with solution of sodium hypochlorite can be effected, and therefore, so that infection can properly be combated? Will it be possible at a later date to remove the packing from the nasal portion of the wound and allow the anterior flap to fall back into position, become adherent and thus successfully block off the intranasal area? These questions could not be properly answered at the time.

Progress Notes.—October 3: At 5 a. m. all of the external dressing was removed. The loose sutures holding the flaps together were removed, and the scalp flaps were gently lifted up. The iodoform gauze packing beneath the flaps was loosened, but none of it was removed. A dressing was so applied as to allow mild herniation. Treatment with solution of sodium hypochlorite was not begun on account of the communication with the nose. The patient's general condition was very good. The pulse rate was 74 and temperature 100.6 F. Mentally the patient was clear and alert. He asked questions about his condition, his left eye, etc. About five hours after his operation he stated that it was the first time in years that he was free from the "old pain" in his head.

At 11 o'clock on the same day the external gauze packing beneath the flaps was loosened and removed. The original iodoform gauze in the depths was not disturbed. There was slight herniation of the brain about the gauze packing in the brain substance and in the abscess cavity, which was as it should be. The head of the bed was elevated to about 15 degrees. The patient's general condition was good, with no rise in temperature and no rigidity of the neck.

October 6: Dressing was done either once or twice a day. Loosening of the two pieces of iodoform gauze, the one in the abscess cavity itself and the other in the extracapsular cavity in the brain substance, was begun. Gauze blocking off the nasal area was not disturbed. The patient's general condition remained good. The temperature varied from 99.8 to 100.8 F., and the pulse rate from 76 to 84. He took his nourishment well, and was mentally alert. The elimination of the bowels was satisfactory.

October 8: All of the original iodoform gauze packings introduced at time of operation, with exception of that blocking off the nasal cavity, were removed. There had been slow and progressive herniation, so that the remnant of the abscess cavity was not more than 1 cm. wide and about 1 cm. deep. The surface of the brain substance had become firmer and more granular. Definite fibrosis had taken place. The small funnel-shaped remnant of the cavity was held open with a wick of iodoform gauze to prevent its collapse in the transverse direction. It was expected that herniation of this remnant of the cavity would be complete by the next day. As soon as it had reached the level of the remainder of the brain surface, herniation could be controlled by catharsis or by lumbar puncture, if necessary. Treatment with solution of sodium hypochlorite had been done for the past two or three days without leakage into the nasal cavity. The patient's general condition remained good throughout. The temperature varied between 99 and 100.5 F., the highest temperature being 100.8 F., on the first postoperative day. At the next dressing the last piece of the original iodoform gauze packing in the nasal and ethmoid regions, which was used to block off these areas, was slowly and completely removed. The surfaces were clean and presented a well granulating appearance. Two narrow iodoform gauze strips were then placed as follows: One was seized with a bayonet forceps through the left side of the nose and was drawn out through the left nares, the distal end being left in the ethmoid region; the other was placed overlying the remnants of the "stalk" or tract of the old abscess cavity so that the ends of the two pieces of iodoform gauze were separated from each other about $\frac{1}{2}$ (1.3 cm.) to $\frac{5}{8}$ (2 cm.) inch. The posterior orbital contents were then allowed to fall back against this area, so that they could become adherent at this site and thus block off the nasal cavity from the operative site of the abscess, i. e., the site of the slight hernia. The remainder of the wound was loosely stuffed with iodoform gauze. Treatment with solution of sodium hypochlorite was discontinued for twenty-four hours, during which time it was expected that the walling-off process would take place and form a barrier between the two operative sites. Otherwise leakage of the solution into the nose would have produced coughing, which would have been detrimental to the hernia. The patient's general condition remained good.

October 9: The patient awakened in the early morning and removed the external dressing. The packings of iodoform gauze were not disturbed. He was slightly irritable, and it is believed that this irritability was due to cortical irritation produced by the dry iodoform gauze in the absence of solution of sodium hypochlorite. Similar episodes had previously been observed in other cases. The condition of the wound was good. The entire exposed surface of the brain was swabbed with a 12 per cent solution of silver nitrate in order to increase the fibrosis. Treatment with solution of sodium hypochlorite was resumed.

October 10: The intranasal gauze strip was loosened but not removed. The general condition of the wound was good. The apex or the remnant of the abscess was somewhat yellowish and was partly separated and slowly coming away. Another suture was placed over the inner canthus fixing the lower flap to the upper one. This suture, in addition to the one previously placed, partially closed the inner portion of the supra-orbital incision.

October 11: Herniation had extended to just above the level of the skull, but not to the level of the scalp. A strip of gauze directed along the old sinus tract toward the nasal area was removed and replaced. Instillation of solution of sodium hypochlorite did not produce coughing, and the solution did not leak into the nose. Therefore, it was considered that the nasal cavity was completely barricaded from the remainder of the wound.

October 20: The wound had been dressed daily. The internal and external scalp flaps had become completely fixed to the lower flap. The granulating surface of the brain was somewhat of the shape of an arrowhead and about 1 inch



Fig. 8 (case 2).—Photograph of the patient on the twentieth day after operation, showing the healed incision through the eyebrow and alongside the nose. There remains a small depressed granulating area which healed on the thirty-fifth day, the day of discharge. The surface of the brain never quite reached the level of the skull.

long in the vertical direction and $\frac{1}{2}$ inch (1.3 cm.) wide. The margins of the wound had become covered with epithelium extending from the edges of the scalp. The small tract overlying the old "stalk" of the abscess, and which extended beneath the medial flap toward the nasal area, was intentionally kept open in order to be assured that no pocketing could take place.

October 22: Epithelization of the granulating surface had increased (fig. 8). Only a small dressing was required. Less frequent instillations of solution of sodium hypochlorite were used. The patient's general condition was good. The temperature varied from 98 to 99 F. and had done so for three or four days. Diplopia was not present. There was only a slight overlapping. The patient had gained weight and was able to receive visitors and use the telephone.

October 29: The wound had almost healed except for the small tract beneath the medial flap over the area of the "stalk." The patient had read the newspaper for four days. On the preceding day he had shaved himself and on the present date he sat up out of bed without any discomfort or dizziness.

November 5: The frontal wound had completely healed except for a small area in the lower inner corner, which was about $\frac{1}{4}$ inch (1.3 cm.) deep and was the remnant of the old tract.

November 7: The patient had been out of bed most of each day. The wound had completely healed, five weeks after the operations. His general and local conditions were good. No headache, dizziness or other complaints developed. The appetite and mentality were good. There was slight edema of the upper left eyelid. A pulsating oval depression, about 1 inch in the vertical direction and about $\frac{5}{8}$ inch (2 cm.) in the transverse direction, was present in the left frontal region. The central portion of the depressed area was about $\frac{1}{2}$ inch (1.3 cm.) below the level of the scalp. The incision through the eyebrow healed kindly, leaving a narrow scar, which was but slightly depressed and produced little deformity. A small patch was to be worn over this area until a plastic operation could be performed on the scalp. The original wound, which was extensive and involved the frontal, ethmoid and intranasal areas, healed more rapidly and with less degree of herniation, without lumbar puncture, than any other which had been observed by us.

The patient was discharged to his apartment on November 8.

Follow-Up Notes.—The patient was seen a few times after his discharge from the hospital, and after a short time he resumed his practice.

On Feb. 16, 1935, a small subperiosteal pocket over the outer margin of the cranial defect was incised with the area under local anesthesia, and two loose pieces of bone wax, which had been used at the time of the original procedure, were removed. There was a small amount of pus about them. The small wound was packed with an azoehloramide oil gauze wick, and after a few dressings it promptly healed.

At the present time the patient has completely recovered. He has no complaints and attends to his practice.

METHOD OF DEALING WITH THE CAPSULE

In case 1 the capsule could not be utilized in any manner in the drainage of the infected lesions in the brain. In fact, had it not been anchored at the site of the perforation in the basilar dura, one would have found it floating in the pericapsular pus, as in case 30 described by Macewen. It was really a foreign body. This is the first and only case in which the capsule has been removed and discarded, and in this instance this was done solely for the reason that no use could be made of it.

In case 2 it was necessary to remove the anterior half of the capsule of the anterior, or older, abscess in order to deal adequately with the coexisting communicating abscess cavity. It was also necessary to remove the anterior half of the "stalk" or tract leading down to the ethmoid bone in order to deal with the infection which it contained. It was not only unnecessary but undesirable to remove the posterior half

of the anterior capsule and its "stalk" for the reason that herniation of the brain at this site would not be advantageous. There was no extracapsular necrotic material at this particular region. The posterior surface of this capsule was firmly fixed to the surrounding brain, and the "stalk" was even more firmly fixed to the dura. The continuation of, this fixation was desired for the following reasons: 1. It was needed to serve as a barrier to prevent infection at this site from entering the subdural and subarachnoid spaces; (2) the heavy thick posterior wall gave additional strength to the brain substance at this point and tended to prevent overdilatation or rupture of the anterior horn of the lateral ventricle, and (3) by prevention of herniation at this site compensatory herniation of the posterior cavity would naturally ensue. It was desirable to have this process occur.

Our expectations and hopes were realized in the manner in which the herniation occurred. That portion of the brain substance which remained after the extracapsular pus and necrotic tissue had been removed by suction, together with the thinner-walled capsule of the posterior abscess, herniated forward just sufficiently to obliterate them. Herniation to the level of the surface of the scalp was not desired and never occurred, even in the absence of lumbar punctures.

In the usual case of uncomplicated, encapsulated abscess of the brain, i. e., in which the capsule is not detached or in which there is no extracapsular necrotic brain substance or pus, only the presenting portion of the capsule should be removed after it has been exposed. The pus in the cavity is removed by suction, and the cavity is wiped out. The inner surface of the capsule is inspected to determine its size and the possibility of an extension into a secondary pocket. It is then gently stuffed or packed with a layer of iodoform gauze placed as a Mikulicz tampon.

The following events then take place: With the oncoming increase in the intraventricular fluid, the floor of the abscess will move outward, delivering the iodoform gauze packing with it. This gauze is gradually removed after being moistened with hydrogen peroxide. The thickened capsule of the abscess then serves as a limiting barrier with definite resistance and tends to prevent overherniation. It also gives greater resistance to the surface of the slight hernia and lessens the likelihood of leakage of cerebrospinal fluid from the ventricle. The capsule is not removed. Its surface becomes covered with granulation tissue and later with epithelium. It becomes a part of the general scar tissue at the operative site.

As soon as the herniation of the cavity has advanced to or about the level of the skull, the probability, or even the possibility, of the formation of a secondary pocket from this abscess does not exist. At

this stage a lumbar puncture should be done if it is necessary, and thereafter it should be repeated sufficiently often to prevent overherniation. The marked herniation advocated and described in my original paper is not necessary and is not desired for the reason that leakage from the ventricle would be more likely and the period of convalescence would be longer. It has been found that herniation can be easily, readily and safely controlled.

My reason for discussing this phase of the subject in this paper is that some writers have evidently concluded that removal of the capsule in toto in the usual case is advocated by me, while others believe that excessive herniation is still advised.

In my last paper it was suggested that the necrotic brain substance found in the early or first stage of abscess of the brain might be removed by suction followed by tamponade of the excavation with iodoform gauze. Two patients with this condition have been operated on in this manner. In each, the lesion was metastatic from a suppurating focus in the lungs. One, a surgeon, has recovered with rapid disappearance of hemiplegia, homonymous hemianopia and hemianesthesia and almost complete disappearance of aphasia. The other is now convalescing in the Bellevue Hospital. These cases will be reported on in a subsequent paper.

SUMMARY

Detailed reports of the pathologic process associated with abscess of the brain, including its variation found at operation or at autopsy, would improve the knowledge of the subject and would help to determine the proper procedure to be used in a given case.

More adequate information concerning the actual condition at operation, especially pertaining to the presence or absence of extracapsular suppuration and necrosis, can better be ascertained by the "open" method of dealing with the abscess than by the "closed" procedure. Some patients, in whom the extracapsular infection is present and on whom the described method of operation is used, would have a better chance of recovery.

Two cases of abscess of the brain associated with extracapsular necrosis and suppuration are reported. Recovery occurred in both cases after operation.

The method of dealing with the capsule is described, and retention of the capsule or a part of it, if possible, is advocated.

Brief mention of operation and the results in two cases of metastatic abscess of the brain is made.

THE INCIDENCE OF GALLSTONES IN SWEDEN

THE CORRELATION OF GALLSTONES WITH VARIOUS DISEASES AND PATHOLOGIC CHANGES

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STOCKHOLM, SWEDEN

Publications have been issued from the different countries regarding the incidence of gallstones and the correlation of gallstones with various diseases. Up to the present there has been no such publication from Sweden, and it was principally for this reason, on the request of Prof. F. Henschen, of the pathologic department at the Karolinska Institute, that I undertook the preparation of this article.

MATERIAL

This treatise embraces the incidence of gallstones observed at autopsy at St. Erik's Hospital, Stockholm, Sweden, during a period of ten years, from the beginning of 1925 to the close of 1934, clinical symptoms observed in cases of gallstones, taken from the records of this hospital, and data on the distribution of the clinical cases of gallstones in Sweden, during the same period, obtained from the annual reports of the public hospitals.

The postmortem study was based on 6,575 autopsies, of which 3,351 were performed on females and 3,224 on males, there being 2 per cent more females than males. Not only was the material equally divided between the sexes, but the records of the cases had been carefully and similarly kept—a valuable factor which renders the material particularly suitable for statistical adaptation.

The clinical reports in the majority of cases were fairly well detailed, but in many instances the histories were scant, and sometimes, owing to the condition of the patient, could not be taken at all. Because of this, the statement of clinical symptoms gathered from the records contained in the clinical reports will be unavoidably limited to some extent. Regarding pregnancy, the reports were too sporadic to admit of any statement as to the correlation with gallstones.

As it is compulsory for each hospital to register carefully all cases of sickness, figures taken from these reports may undoubtedly be

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regarded as an exact recording of the incidence of gallstones at that particular hospital. As to whether or not they should be considered as demonstrating the incidence of gallstones in that particular neighborhood will be dealt with when I consider the results of my investigation.

METHOD

The investigation was executed tabular-statistically, i. e., all cases of gallstones were tabulated for each year and each case in which autopsy was performed has been recorded as to (*a*) the age and sex of the patient; (*b*) the type, number, size and position of the stones; (*c*) the contemporary changes in the bile, gallbladder and biliary ducts, and (*d*) other diseases and changes of interest (constitutional diseases, disturbances in the transformations of calcium and pigment, disturbances in motility in the bile ducts and in connection with the local and general circulation, local and general infectious diseases, malformations, etc.). Clinical symptoms have been recorded in each case as to (*a*) the sex of the patient and the time when each symptom appeared; (*b*) whether the symptom appeared once or whether it was repeated and (*c*) whether, as regards the patient in question, only one symptom occurred; if more, the order of appearance, and whether they recurred in immediate sequence or at intervals. These data should be considered as preliminary material.

A part of the investigation as to the incidence of gallstones at St. Erik's Hospital and the distribution according to age is based on material recorded at this hospital from 1925 to 1932, collected by Dr. T. Bruce, of Stockholm.

INCIDENCE OF GALLSTONES IN STOCKHOLM,

From table 1 it is seen that gallstones have been found frequently at autopsy at St. Erik's Hospital. However, as the patients were older (chart 1), the figures shed no light concerning the incidence of gallstones among the inhabitants of Stockholm in general. I have therefore calculated the percentage of incidence within the various age groups, i. e., from 0 to 15 years, from 15 to 50 years and after 50 years, and I have obtained records from Stockholm's Statistical Bureau as to the average number of inhabitants of both sexes in Stockholm within the aforementioned age groups for the years from 1925 to 1934, inclusive. Thus, taking into consideration age and sex, I have been able to estimate the incidence of gallstones among the inhabitants of Stockholm as follows: Of the 551,618 inhabitants, 58,205 should have gallstones, i. e., 10.5 per cent. Accordingly, every tenth inhabitant of Stockholm should have gallstones.

CLINICAL SYMPTOMS

How many patients with gallstones manifest clinical symptoms?

Clinical symptoms were noted in approximately 25 per cent of the patients, i. e., in 4.9 per cent of those who came to autopsy. The incidence in males and females was relatively equal. Death ensued in 6.4 per cent of the cases of gallstones (with complications), i. e., 1.2 per cent of the cases in which autopsy was performed. Fatalities occurred in 5.5 per cent of the females, i. e., in 1.5 per cent of the females who came to autopsy, and in 8.3 per cent of the males, i. e., in 1 per cent of the males who came to autopsy. According to the calcu-

TABLE 1.—*Incidence of Gallstones, Cited from the Autopsy Records at St. Erik's Hospital*

Year	Autopsies			Cases of Gallstones					
				Females		Males		Total	
	Females	Males	Total	Num- ber	Per- centage	Num- ber	Per- centage	Num- ber	Per- centage
1925.....	221	240	461	54	30.3	13	5.4	67	14.5
1926.....	271	286	557	82	30.3	31	10.8	113	20.3
1927.....	339	333	672	61	18.0	30	9.0	91	13.5
1928.....	276	310	586	62	22.5	21	6.8	83	14.2
1929.....	286	304	590	71	24.8	38	12.5	109	18.5
1930.....	365	331	696	115	31.5	49	14.8	164	23.5
1931.....	392	358	750	106	27.0	52	14.5	158	21.1
1932.....	399	354	753	108	27.0	44	12.3	152	20.2
1933.....	362	328	690	121	33.4	59	18.0	180	26.1
1934.....	440	380	820	123	28.0	48	12.6	171	20.8
10 years.....	3,351	3,224	6,575	903	27.0	385	12.0	1,288	19.6

Incidence of gallstones in the whole material: 19.6%, i. e., in every fifth case
 Incidence of gallstones in females: 24.0%, i. e., in every fourth case
 Incidence of gallstones in males: 12.0%, i. e., in every eighth case
 Proportion of incidence in females and males: 2:1

lation of incidence among the inhabitants of Stockholm, 2.5 per cent of the inhabitants, or one fortieth, had symptoms.

Records of clinical symptoms have been obtained, as stated previously, from the histories of patients who came to autopsy. With due allowance for inaccurate notation of symptoms, for obvious reasons I will refrain from attaching too much importance to the figures as regards either the total incidence of the clinical symptoms or the incidence of the separate symptoms. As regards the latter, the figures so decidedly point in a certain direction that I cannot refrain from drawing attention to them.

Various Symptoms and How They Appear.—As may be seen from table 3, "typical painful attacks" were the most frequently recorded symptom. They were present in 217 patients, and in 22, or one tenth, they were the only symptom. In 170 of the 217 patients, or eight tenths,

signs of cholecystitis and cholangitis developed sooner or later. The latter symptoms appeared as a rule in immediate connection with "typical painful attacks." In those persons in whom "typical painful attacks" were the only symptom it was exceedingly common for only one attack

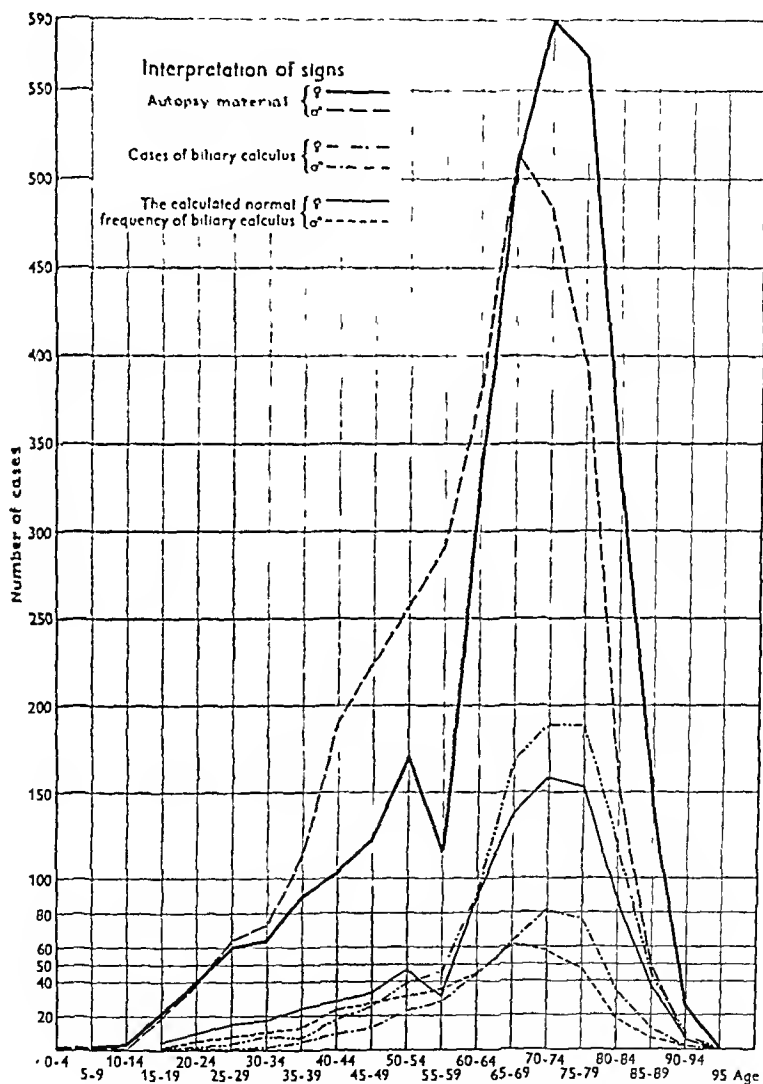


Chart 1.—The distribution of autopsy material and cases of biliary calculus according to age and sex.

to occur during the patient's life, while in persons in whom signs of cholecystitis and cholangitis later appeared more frequent attacks were the rule. In the majority of those who had only one "typical painful attack," there developed later signs of cholecystitis and cholangitis.

TABLE 2.—*Clinical Symptoms in Cases of Gallstones According to Hospital Records*

Cases of Gallstones				Clinical Symptoms						Cause of Death					
			Total	Females		Males		Total		Females		Males		Total	
Year	No.	No.		No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
1925	54	13	67	16	29.6	1	7.9	17	25.4	3	5.6	3	4.5
1926	82	31	113	13	15.8	4	12.9	17	15.0	1	1.2	1	3.2	2	1.8
1927	61	30	91	18	29.5	10	33.3	28	30.8	5	8.2	2	6.7	7	7.7
1928	62	21	83	26	42.0	9	42.9	35	42.5	6	9.7	1	4.8	7	8.4
1929	71	38	109	14	19.7	14	37.0	28	25.7	3	4.2	7	18.4	10	9.2
1930	115	49	164	26	22.6	11	22.4	37	22.6	8	7.0	5	10.2	13	7.9
1931	106	52	158	27	25.5	7	13.5	34	21.5	6	5.7	2	3.8	8	5.1
1932	108	44	152	25	23.1	8	18.2	33	21.7	4	3.7	5	11.4	9	5.9
1933	121	59	180	36	30.0	16	27.1	52	28.9	7	5.8	7	11.9	14	7.8
1934	123	48	171	26	21.1	12	25.0	38	22.2	7	5.7	2	4.2	9	5.3
10 yr.	903	385	1,288	227	25.1	92	24.0	319	24.9	50	5.5	32	8.3	82	6.4

TABLE 3.—*Various Clinical Symptoms**

Symptom	Total No. of Cases	Sole Symptom	Sex; No. of Cases	Manner of Appearance	
Typical painful attacks	217 (68%)	22 (6.9%)	♀	{	Sole symptom.....20 { 1 attack in 16 cases several attacks in 4 cases
					Combined with cholecystitis and cholangitis.....99 { 1 attack in 28 cases several attacks in 71 cases
					Combined with dyspeptic trouble.....19
			♂	{	Sole symptom.....2 { 1 attack in each case
Movement pains	2 (6%)	1 (3%)	♀	{	Combined with cholecystitis and cholangitis.....71 { 1 attack in 16 cases several attacks in 55 cases
					Combined with dyspeptic trouble.....6
					Sole symptom.....1 { several attacks
			♂	{	Combined with cholecystitis and cholangitis.....1 { several attacks
Signs of cholecystitis and cholangitis	189 (59%)	18 (5.6%)	♀	{	Sole symptom.....13
					After "typical painful attacks".....99
					Sole symptom.....6
			♂	{	After "typical painful attacks".....71
Dyspeptic troubles	109 (34%)	53 (16.7%)	♀	{	Sole symptom.....51
					Combined with other symptoms.....47
					Sole symptom.....2
			♂	{	Combined with other symptoms.....9

* Only one symptom developed in 29.3 per cent of the patients. Several different symptoms occurred simultaneously or one after the other in 70.7 per cent of the patients.

Thus it would seem possible that if the patient had "typical painful attacks," cholecystitis and cholangitis were almost sure to follow.

In only 18 of 189 patients have signs of cholecystitis and cholangitis been noted without any record of previous "typical painful attacks." As to whether cholecystitis and cholangitis can develop without the preceding typical painful attacks as a symptom of the passing or wedging in of the stone, I dare not venture an opinion in view of the aforementioned inaccuracies.

With reference to dyspeptic troubles, it would seem just as impossible to make any statement, because, as has been seen, these need not necessarily have been brought about by gallstones but may have been a symptom of some associated disease.

A symptom has been included here which might be called "movement pains." As the name implies, the term indicates those pains which occur and accompany movement and which disappear when the patient is in repose. They are manifest as light pains or as diffused discomfort in the region of the gallbladder and eventually in the back at the angle of the right scapula or between the right shoulder blade and the spine, or they may occur simultaneously at both places or at only one of them. On careful investigation of the histories of patients with gallstones I have found "movement pains," as I remember now, in 8 of 15 patients. These pains were the patient's earliest symptom of gallstones, and when they appeared there was no sign of infection. This is essentially the reason I have included this symptom in this connection. It has been noted in only 2 patients in this study, and this is probably because the patients had not taken notice of those lesser inconveniences and therefore omitted to mention them to the doctor who took the history. (The diagnosis in both cases was lumbago [?]).

DISTRIBUTION OF MATERIAL ACCORDING TO AGE

When the postmortem material was grouped according to age a well known condition prevailed; namely, the mortality rate was higher in men than in women in the early years, i. e., between the ages of 30 and 55, while it was higher in older women. It is of particular interest to note that the greater part of this material includes persons between 60 and 80 years of age. The distribution of gallstones according to age will be taken up in connection with the question as to at what age stones appear and as to how long new stones can be formed.

In order to determine at what age stones appear and how long new stones may be formed, obviously a comparison must be made between the incidence curves in clinical cases and the normal incidence curves calculated according to the age distribution in the postmortem

material (chart 1). An investigation of chart 1 shows that stones have been known to appear at an early age (even a child may be subject to the complaint), but they occur especially in persons of more advanced years, in this case in those approximately between the ages of 40 and 60. Obviously the line cannot be drawn more narrowly concerning a chronic complaint such as gallstones. Therefore the age limits given here are intentionally relatively wide.

The incidence of gallstones according to age is found to differ as regards sex. Stones appear to occur in men only sporadically before the age of 50 years; they develop as a rule between the ages of 60 and 65 and up to 85 and 90. One finds, further, that the relative increase of observed incidence as against the calculated average incidence increases progressively, so that at the period between 75 and 79 it is 60 per cent, between 80 and 84, 75 per cent, and between 85 and 89, 100 per cent. After the ages of 85 to 89, the relative increase diminishes. From this it would seem that new stones may continue to appear at least up to the age of 85. In other words, one might say that in men new stones can form at least up to the age of from 80 to 85 years. In women the first small increase in incidence occurs between the ages of 25 and 35 years, and the second, between the ages of 45 and 55. Probably these increases are associated with the first pregnancy and with the climacteric. That there is no increase in men within those age periods argues in favor of this assertion. Strictly speaking, stones seem to make their real appearance in women between 50 and 55 and between 80 and 85 years. At these ages incidence curves in clinical cases may be seen to exceed the calculated average curves. The relative increase as against the calculated average in women goes on to from 80 to 84 years, when it is 37 per cent. Judging from this, it would seem that in women gallstones can form at least up to 75 and 80 years of age.

INCIDENCE VARIATION DURING DIFFERENT PERIODS

It has been seen from table 1 that the incidence of gallstones varies during the years. In reference to a complaint such as gallstones, in which stones have been known to lie ten years or more in the gallbladder without causing death or giving rise to a symptom which compelled the patient to go to a hospital, one is obviously unable to pay attention to the separate yearly variations but must take longer periods into consideration. I have chosen periods of three years, fully aware that the time is short, but this choice is due to the fact that this investigation comprises only a period of ten years. An illustration of the results of this investigation is shown in chart 2.

From this chart it may be seen that there has been a steady increase in the incidence of gallstones in women and men during the last ten years in Stockholm. In order to illustrate still further how the complaint varies in its incidence in a decided manner during certain periods, I have included in chart 2 the incidence curves in postmortem material from Rostock, Germany, during the years 1911 to 1925.¹

A study of this material shows how during the years of the World War and the following years, to the close of 1922, the incidence diminished, especially in women. To what this is due it is impossible to say definitely, as the report lacks a statement as to the total age and sex incidence during the period in question. It is conceivable, however, that during these years there occurred a general decrease in the average age

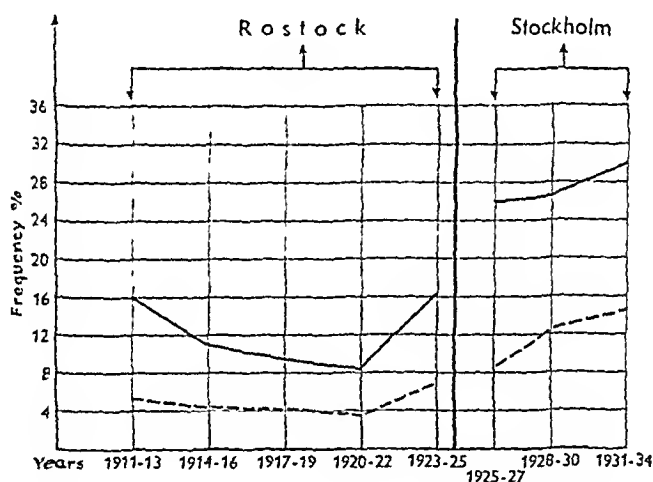


Chart 2.—The frequency of biliary calculus in Rostock, Germany, and Stockholm, Sweden, during the years 1911-1934.

of patients who came to autopsy, and as stones belong more especially to age than to youth, a natural explanation may be found here for the diminution in question. It would seem reasonable that the decrease in age of patients who came to autopsy should have been manifested equally in the sexes, or rather more in men, which was not the case. It is not unlikely, moreover, that the decrease was due to impaired nutrition during these years of dearth, when one considers the existence of a definite correlation between lipomatosis and certain types of stones (tables 5 and 6). This is further supported by the fact that the decrease occurred mostly in women, when it is remembered that it is especially

1. Schretzenmayr, Annemaria: Gallensteinleiden und Konstitution, *Ztschr. f. Konstitutionslehre* 13:792, 1928.

women in a position to enjoy nutritious food who are liable to have lipomatosis.

DISTRIBUTION OF GALLSTONES IN SWEDEN

When one knows that the incidence of a certain disease, and perhaps of gallstones in particular, at a certain hospital depends on a number of factors, including the correctness of the diagnosis, the surgeon's repute and the mentality of the inhabitants of the neighborhood (as to whether they often seek medical advice or not), there are possibilities that the result of this investigation may not exactly correspond with the real state of affairs. On the other hand, I feel obliged to avail myself of these annual reports from the public hospitals, as they afford the only material on which to base a study.

TABLE 4.—*Distribution of Stones According to Sex and Type*

Type of Stone*	P.		Ch.		P-Ch.		P-C.		P-Ch-C.	
	♀	♂	♀	♂	♀	♂	♀	♂	♀	♂
Solitary.....	15	12	43	13	13	5	12	12	43	5
1 group.....	76	56	2	..	24	3	68	24	85	27
2 groups.....	8	8	1	..	6	1	29	19	54	19
3 groups.....	2	1	3	..	4	4	10	7
4 groups.....	2	..
Gravel.....	3	1	2
Enclosed stone.....	1	1	1	2	2	6	4
Total.....	104	78	46	13	46	9	115	59	194	61
	(57%)	(43%)	(78%)		(83%)		(66%)		(76%)	
	182		59		55		174		255	
	(25%)		(8%)		(7½%)		(24%)		(35%)	

Enclosed stone in 17 cases, i. e., 2.34% of the total cases of gallstones

* P. indicates a pure pigment stone; Ch., a pure cholesterol stone; P-Ch., a mixed pigment and cholesterol stone; P-C., a mixed pigment and calcium stone, and P-Ch-C., mixed pigment-cholesterol-calcium stone.

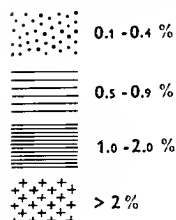
It is evident from chart 3 that stones occur on the whole more frequently in South Sweden (Svealand and Götaland) than in North Sweden (Norrland). Norrland is mostly a mountainous district, while Svealand and Götaland consist mostly of fertile, lowland tracts. Also it will be seen that the incidence is especially great in the neighborhood of Örebro (a relatively rich town on a fertile plain in Svealand) and on the fertile plain of Östergötland (South Sweden), while it is obviously inconsiderable on the rocky moorland districts of Småland and the Västgöta heath. One finds the lowest incidence in the fishing villages of Bohuslän and Blekinge (South Sweden) and in the barren districts of Kolmården, Bergslagen and Norrbotten (North Sweden). It would thus seem as if cases of gallstones are more numerous in rich and fertile districts and of rarer occurrence in poorer and more barren areas.

TABLE 5.—Diseases and Changes with Observed and Actual Correlation with Gallstone

Disease	Incidence			Observed			Combined with Gallstone				Calculated Actual Correlation*		
	Females	Males	Total	Females	Males	Total	Females		Males		Total		
							No.	%	No.	%	No.	%	%
Cholecystitis, acute.....	253	159	412	10	13	23	151	7	101	4	261	3	9
Cholecystitis, chronic.....	114	60	174	22	123	315	61	5	22	2	87	5	62
Disturbances in flow of bile.....	36	6	42	22	30	121	11	2	0	0	10	2	47
Cancer of gallbladder.....	15	11	26	8	1	9	1	1	0	0	1	1	8
Cancer of bile ducts.....	101	60	161	15	7	22	6	4	18	5	24	7	1
Lipomatosis vesicular follicles.....	103	252	357	34	18	82	6	4	1	0	7	5.2	1
Cirrhosis of the liver.....	218	...	218	59	50	109
Tumored liver.....	41	25	66	14	3	17	3	3
Tumor, principally cancer of pancreas	24	11	35	8	1	9	2	2
Cancer of head of the pancreas.....
Enteritis, enterocolitis.....
Pneumonia.....	430	378	808	348	187	535	202	9	112	6	317	11	42
Hypertrophic gastritis.....	1,021	1,014	2,035	271	103	436	13	9	13	9	26	6	1
Lipomatosis universalis.....	330	141	471	113	30	179	54	8	19	4	73	15	17
Lipomatosis pancreatica.....	370	273	643	128	63	201	91	8	30	5	121	10	18
Lipomatosis hepatica.....	33	22	60
Diabetes mellitus.....	132	85	217	53	23	78	17	5	15	3	32	6	14
Xanthomatosis mesenterii.....	7	9	16	3	3	6	2	1	2	1	3	1	13
Lipomatosis adrenalis.....	101	133	239	53	34	92	13	5	18	4	31	7	9
Cancer.....	1,239	154	64	218
Cardio-arteriosclerosis.....	6,031	753	297	1,050
Tuberculosis, acute progressive.....	1,947	66	49	117
Tuberculosis, healed and chronic in-
duration.....	548	833	1,401	248	112	391	100	9	12	5	116	13	7
Tuberculous calcification.....	345	137	482	106	37	143	14	8	42	4	73	7	18
Calcification (tuberculous excepted)	223	46	269	53	5	58	13
Osteoporosis.....	36	19	55	22	8	30	13	3	6	1	19	3	29
Periosteal anemia.....	126	15	14	29
Anemia universalis.....	79	18	16	34	10	2	10	2	19	3	20
Hemorrhosis of the liver.....	32	47	79
Stasis of portal vein.....	1,608
Stasis of the liver.....	1,184	242	100	351
Fibrosis testis.....	230	...	46	46
Hypertrophic prostatitis.....	682	...	130	130
Struma colloidosa (adenomatous).....	210	38	248	68	8	76	11	6	19	3	119	12	13
Cystic ovarii.....	300	...	300	49	...	49	49	7	119	12	6
Tumor uteri (benign).....	1,186	297	...	297	4	2	49	7	6
Diverticulum of intestine (except jux-
tapapillare).....	62	25	87	20	5	25	3	3	2	2	8	4	...
Diverticulum juxtapapillare.....	58	36	94	27	13	40	11	3	9	2	22	4	19.1
Hernia.....	195	2	16	18
Malformations.....	516	401	917	144	54	198	5	9	6	6	18	11	...

* In the column "Calculated Actual Correlation," a minus sign has been used in those instances in which the correlation was negative. The correlation was positive but not statistically sure ($3 \times \chi$ are not $>$ the calculated correlation) in the following conditions: acute cholecystitis, cirrhosis of the liver (females), lipomatosis adrenalis (females), tuberculous, healed and chronic induration (male), calcifications, tuberculous excepted (females), and struma colloidosa adenomatosa (males).

Interpretation of signs (% of number of cases recorded)



 Minimum

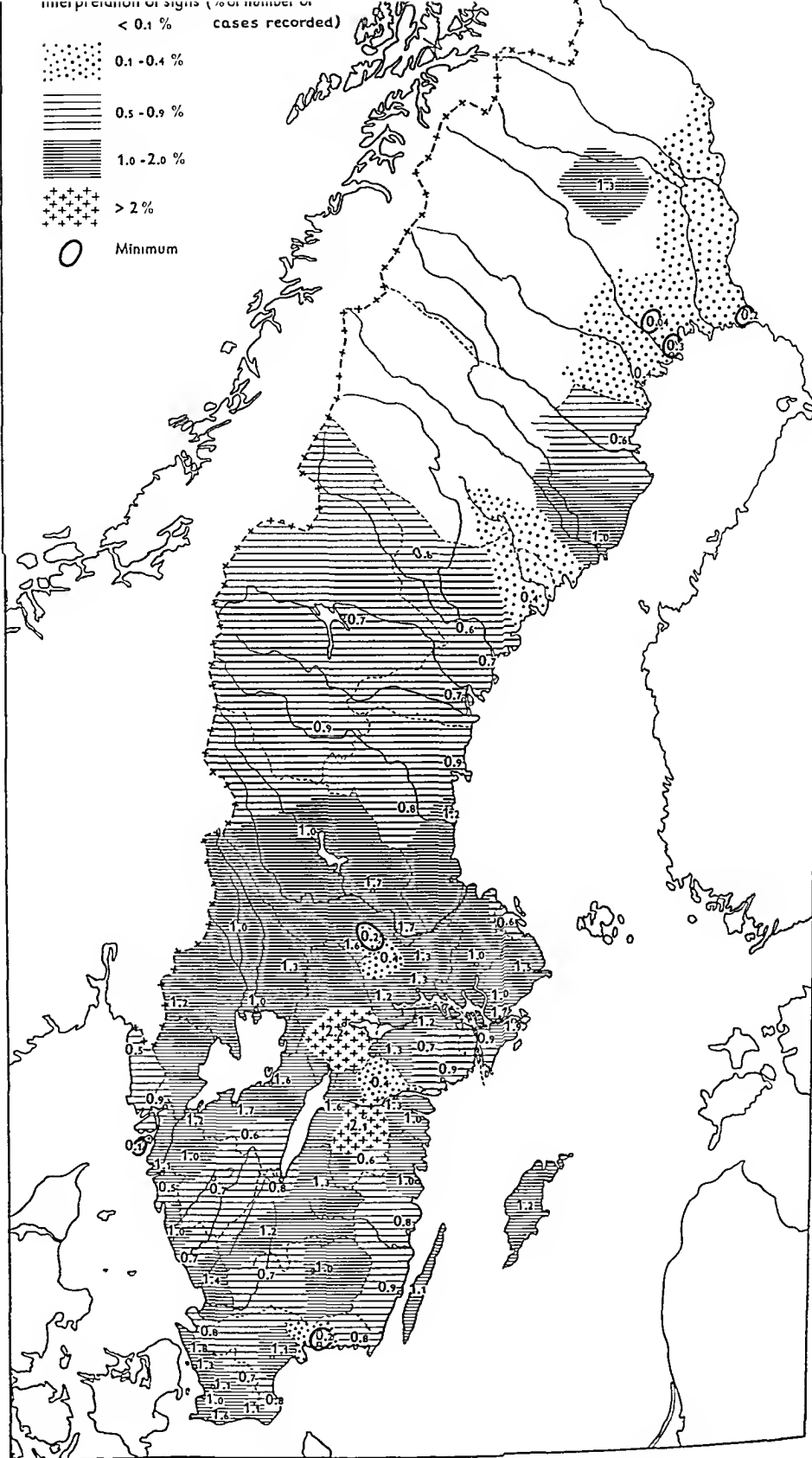


Chart 3.—The distribution of gallstones in Sweden.

DISTRIBUTION OF THE VARIOUS TYPES OF STONES

The distribution of the stones according to sex and type is given in table 4.

Of the various types of stone, the mixed pigment-cholesterol-calcium stone is the most common. This type was present in about one third of the whole group of material. The pure pigment stone and the mixed pigment and calcium stone comprised each about one fourth of the group, while those of rarest occurrence, the pure cholesterol stone and the mixed pigment and cholesterol stone, comprised about one twelfth of the whole.

TABLE 6.—*Distribution of Stones According to Disease*

	Pigment Stones				Cholesterol Stones				Calcium Stones				Total No.
	Pure		All Stones		Pure		All Stones		P.C.		P.Ch.C.		
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	
Normal.....	182	23.1	666	91.9	59	8.1	369	50.9	174	20.0	225	35.2	725
Cholecystitis, acute.....	1	6	1	14.3	5	71.4	1	4	57.1	7
Cholecystitis, chronic.....	24	153	17	10.0	99	58.2	47	27.6	72	42.4	170
Disturbances in motility of bile ducts.....	18	29.0	54	8	12.9	31	13	17	62
Cancer of gallbladder.....	1	9	2	18.2	8	72.7	2	5	45.5	11
Cancer of bile ducts.....	0	3	1	25.0	4	100.0	0	2	50.0	4
Cirrhosis of liver.....	28	35.9	72	92.3	6	37	13	30	38.5	78
Hemosiderosis of liver.....	10	62.5	16	100.0	0	1	5	31.3	0	16
Pernicious anemia.....	10	55.6	18	100.0	0	4	4	4	18
Lipomatosis universalis.....	19	97	12	11.0	59	54.1	31	28.4	34	109
Lipomatosis pancreatica.....	6	51	8	13.6	47	79.7	6	37	62.7	59
Diabetes mellitus.....	10	39	92.9	3	22	52.4	10	14	42
Xanthomatosis, mesenteric.....	3	60.0	5	100.0	0	1	1	1	5
Lipoidosis adrenalis.....	15	51	7	12.1	25	18	31.0	16	58
Tuberculosis, healed.....	62	223	92.9	17	118	60	25.0	80	240
Tuberculous calcification.....	23	106	96.4	4	47	40	36.4	34	110
Calcification.....	48	190	96.4	7	84	65	33.0	56	197
Fibrosis testis.....	10	43.3	20	3	13.0	10	3	5	23
Hypertrophla prostatae.....	30	43.2	65	6	23	18	25.4	14	71
Struma colloidosa.....	10	48	96.0	2	29	58.0	11	17	50
Diverticulum juxtaapillare....	14	40.0	9	1	10.0	5	1	2	10
Pneumonia.....	48	36.9	126	96.9	4	63	19	57	43.9	130

Distribution according to sex indicates that on the basis of percentage, and also absolutely, the pure pigment stone is the most common in men while the pure cholesterol stone and the mixed pigment and cholesterol stone, according to percentage, are most common in women.

In addition to the existing differences between the pure cholesterol stone and the pigment stone, still another difference comes to light when one investigates the distribution of stones in regard to size. Pigment stones appear multiply as a rule and are variable in size, while pure cholesterol stones generally occur singly. Nevertheless, as table 4 indicates, pure cholesterol stones in a few cases have even appeared in

variable size, a coincidence of special interest when one remembers statements as to the metamorphosis of gallstones through special cholesterol processes, as set forth in the literature. Meckel von Hemsbach seems to have been the first to have made this observation. Later Boysen² and Naunyn³ investigated further and proved the correctness of these observations. The metamorphosis⁴ implies that a quantity of already formed pigment-calcareous concrement collects dissolved cholesterol if allowed to remain in the gallbladder and bile ducts any length of time. The dissolved cholesterol (the presence of bile acids is necessary to dissolve the cholesterol) expels the calcium, which, by means of the weak acids, is brought into a dissolved condition. By this process the cholesterol is separated and precipitates into its colloid form, which later, according to Ostwald's *Reifungsprinzip*, becomes crystallized and is known as typical cholesterol crystals. Thus it is seen how certain pigment-calcium stones can be entirely transformed into pure cholesterol stones. However, according to Naunyn, a distinction must be made between cholesterol stones thus formed and the so-called primary crystalline cholesterol stones, which, it would seem, are formed from a primary nucleus of crystalline cholesterol and, in distinction from the cholesterol stones, have a nucleus clearly defined from its surroundings. This observation is made in order to explain that not all pure cholesterol stones (according to present knowledge) develop from mixed pigment and calcium stones and, in addition, to explain that the following argument must be confined to certain pure cholesterol stones.

In consideration of this metamorphosis, one is tempted to believe that pure cholesterol stones, in some cases, appear in variable size as remains from the time when they already existed as mixed pigment and calcium stones. In other words, it would imply that some, at least, of the pure cholesterol stones were mixed pigment and calcium stones of years' standing.

DISEASES AND PATHOLOGIC CHANGES WHICH HAVE ACTUAL CORRELATION WITH GALLSTONES

To determine which diseases have an actual correlation with gallstones I have made note of the diseases and pathologic changes which, when investigating postmortem material, I found combined with stones;

2. Boysen, J.: Ueber die Struktur und die Pathogenese der Gallensteine, Berlin, S. Karger, 1909.

3. Naunyn, B.: Die Gallensteine, ihre Entstehung und ihr Bau, Jena, Gustav Fischer, 1921.

4. Naunyn,³ p. 23.

also, I have ascertained the number of diseases and to what extent they were found in connection with gallstones. In addition, I have statistically calculated how many chance combinations might conceivably appear (i. e., assuming no existing correlation between gallstones and the disease in question). By subtracting the number of chance combinations from the number of observed combinations and by calculating and making due allowance for the average miscalculation, I have succeeded in obtaining the figures for an actual correlation. The results are shown in table 5.

Cholecystitis, Especially the Chronic Type (in Approximately 60 Per Cent of the Cases).—It is not possible to determine from these statistics whether cholecystitis may be considered primary or secondary to gallstones. Clinical experience teaches, of course, that symptoms of cholecystitis appear after signs that a stone has become lodged, i. e., after the stone already exists. The report on clinical symptoms (table 3) argues in favor of this, and so, to some extent, does the correlation between the various diseases and the different types of stones (table 6), which indicates that it is especially the larger (older) types (pure cholesterol stones, mixed pigment and calcium stones and mixed pigment-cholesterol-calcium stones) which manifest decided correlation with cholecystitis. That it is mainly chronic cholecystitis which occurs in this association with gallstones may be assumed to be due to the irritation caused by the stones in the bladder maintaining an inflamed condition, which becomes chronic. Against the theory that infection should be a primary factor in the formation of stones there are reported in the literature cases of infection of the gallbladder, cholecystitis and disturbances in the motility of the bile of many years' standing without the formation of stones.⁵ But, as previously mentioned, it is impossible to make any definite statement.

Disturbances in Motility in the Biliary Ducts (in Approximately 50 Per Cent of the Cases).—It is not possible here to regard a priori those disturbances in the motility of gall as primary to the formation of stones. It is true that in most of the literature stress is laid on the theory that such a disturbance disposes to the formation of gallstones, but I have nowhere found evidence to support this assertion. Should one assume a disturbance in motility to be primary, a decided correlation will be seen between severe sclerosis of the head of the pancreas or other processes there, which deform the ductus choledochus and thus hinder the normal emptying of bile. No such correlation is indicated, however, throughout this relatively large amount of material. It is not

5. Törnqvist, G. W.: Beiträge zur Pathologie und Therapie der Gallenstein-krankheit, Stockholm, P. A. Norstedt & Söner, 1903, pp. 21-22.

out of the way to believe that stones, through mechanical irritation or indirectly through inflammation, give rise to cicatrization and strictures in the biliary ducts, with the attendant hindrance to the emptying of bile. Only incontestable experiments, however, can solve the problem as to the correlation between a disturbance in motility in the biliary ducts and the formation of gallstones. Such experiments have been made, but up to the present, as far as I know, have not given positive results.

Tumors, Especially Cancer in the Gallbladder and Bile Ducts (in Approximately 40 and 8 Per Cent of the Cases, Respectively).—These conditions will be considered later in connection with their correlation with the various types of stones.

Certain Disturbances in the Metabolism.—The following disturbances in metabolism were encountered: (a) lipomatosis universalis (in approximately 17 per cent of the cases and lipomatosis pancreatica (in 18 per cent of the cases); (b) diabetes mellitus (in approximately 14 per cent of the cases); (c) lipoidosis adrenalis (in approximately 9 per cent of the cases); (d) xanthomatosis mesenterii, of which there were only sixteen cases included in the whole of the material, consequently the calculation of correlation will be uncertain.

With certain reservation for diabetes, it might in all probability be considered unlikely that these disturbances of metabolism are due to gallstones or any of the complications, but it is likely enough that these, or other factors connected with their appearance, occurrence or disappearance, favor the origin or further formation of stones. I shall return to this factor when dealing with the types of stones having a correlation with lipomatosis.

Calcification of Different Kinds, Especially Tuberculous Calcification (in Approximately from 15 to 20 Per Cent of Cases) and Healed Tuberculosis (in 7 Per Cent of the Cases).—It is already known that healed tuberculosis is combined with gallstones more often than active or acute tuberculosis. From this it has been understood that tuberculosis in a case of gallstones more often takes on a mitigated form and evinces a greater tendency toward healing than when gallstones are not present.⁶ This conclusion is, however, not quite correct, because, as will be shown later, the correlation applies not to gallstones in general but only to certain types (table 6). This report also indicates that it is especially the tuberculous calcification which has a correlation with gallstones, and when one sees, further, that pathologic calcification as a rule manifests almost as great a correlation with gallstones, the explanation might

6. Boysen,² p. 795.

assumably be that it is the tendency to calcific precipitation in the various pathologic processes which brings about the correlation.

Pernicious Anemia and Hemosiderosis of the Liver (in Approximately 29 and 20 Per Cent of the Cases, Respectively).—Table 5 illustrates how a calculated correlation occurs between pernicious anemia and gallstones in sixteen cases. A similar illustration is given of sixteen cases of hemosiderosis of the liver and gallstones. There were sixteen cases of pernicious anemia and hemosiderosis of the liver in the material. It may, of course, be incidental that the figures in these cases coincide. It is conceivable also that in those cases in which pernicious anemia manifests a pathologico-anatomic hemosiderosis of the liver, the possibility of or disposition to formation of gallstones is great. It is of special interest, and an account of the same will be given later, that hemosiderosis of the liver in just sixteen cases, i. e., the total number of cases, shows a decided correlation with a certain type of stone. This repudiates the idea that the report previously cited may be a coincidence.

Stasis of the Liver and of the Portal Vein (in Approximately 9 and 13 Per Cent of the Cases, Respectively).—An explanation of the correlation between these complaints and gallstones can obviously not be speculated on without experiments. As earlier experiments seem to indicate that the formation of a concretion is dependent on a change in the p_H of the bile,⁷ it should not be considered out of place to ask whether a local stasis can change the p_H of the bile.

Cirrhosis of the Liver (in Approximately 1 Per Cent of the Cases), Fibrosis Testis (in Approximately 6 Per Cent) and Hypertrophica Prostatatae (in Approximately 6 Per Cent).—At first sight, undoubtedly, it would appear somewhat unreasonable to assume the existence of a correlation between fibrosis testis and hypertrophica prostatatae, respectively, and gallstones. But Henschen and Bruce⁸ have drawn attention to a certain parallelism in the appearance of cirrhosis of the liver and fibrosis testis. In addition, as cirrhosis of the liver in men (5 per cent) and fibrosis testis show practically the same correlation with gallstones in this material (13 and 14 per cent, respectively), the correlation with gallstones must obviously be due either to some possible common cause or to the parallel diseases, cirrhosis of the liver and fibrosis testis or to cirrhosis of the liver alone. From the report on the correlation of these

7. Hanser, Rob: Gallensteinkrankheit, in Henke, F., and Lubarsch, O.: Handbuch der speziellen pathologischen Anatomie und Histologie, 1929, Berlin, Julius Springer, vol. 5, no. 2, p. 801.

8. Henschen, F., and Bruce, T.: Ueber die Häufigkeit und Formen der Lebercirrhose in Stockholm, Compt. rend. première conf. internat. de path. géog. 1:249, 1931.

diseases to certain types of stones (see table 6), it may be gathered that both diseases show a decided and similar correlation with a certain type of stone. This correlation speaks for a common factor in the formation of stones.

Pneumonia (in Over 40 Per Cent of the Cases).—This condition has shown a decided and great correlation with gallstones. It is well to adopt a skeptical attitude, however, in this connection, as pneumonia is one of the commonest immediate causes of death, and when studying the reports it is difficult in some cases to discriminate; therefore, statistical calculations, to some extent, are unavoidably misleading. In only those cases in which at autopsy lumps of pigment were found, which to all appearances were formed shortly before death, was pneumonia included. Thus the correlation (according to table 6) between pneumonia and pigment stones may be misleading.

Struma Colloides (Adenomatosa) (in Approximately 8 Per Cent of the Cases).—It is remarkable how frequently at autopsy struma colloides and adiposity have been found synchronously. I cannot, of course, assert that this particular adiposity was responsible for the correlation, but I am inclined to believe that such is the case. According to the modern endocrinologic theory that a colloidal hypertrophic struma is the outcome of hypofunction of the thyroid gland, slow combustion in the body with a tendency to adiposity might be assumed. When it is understood that a decided correlation exists between pathologic adiposity and gallstones, a feasible explanation should be found as to the correlation between colloidal struma and gallstones, and in these cases the simultaneous and relatively frequent lipomatosis.

CORRELATION OF VARIOUS DISEASES AND PATHOLOGIC CHANGES WITH THE DIFFERENT TYPES OF STONE

It is stated that diseases and pathologic changes showing decided correlation with gallstones also have a decided correlation with a certain type of stone (table 6).

I shall touch on only the most important results of my investigation. These show the diseases and pathologic changes which manifest a calculated absolute correlation with certain types of gallstones.

1. Pure pigment stones were found associated with pernicious anemia, hemosiderosis of the liver, cirrhosis of the liver, fibrosis testis and hypertrophia prostatae.

Since fibrosis testis, hypertrophia prostatae and cirrhosis of the liver are diseases which appear mostly in men, their absolute correlation with pure pigment stones should afford an explanation as to why this type of stone is found (on the basis of percentage) more generally in men than in women (table 4).

As far as pernicious anemia and hemosiderosis of the liver are concerned, reasoning in connection with their relationship to gallstones has led one to believe that in all probability it is only in cases in which pernicious anemia gives rise to hemosiderosis of the liver that the disposition to gallstones arises. Thus, it can be said that hemosiderosis of the liver is the deciding factor for a disposition toward the formation of stones. When it is seen that pigment stones appear in every case of hemosiderosis of the liver (table 6) and that in a vast number of cases (62.5 per cent) these are pure pigment stones, one has every reason to believe that it is the excess of pigment in the liver indicated by hemosiderosis which is responsible for the disposition to stone formation.

2. Pure cholesterol stones were found associated with cancer of the gallbladder and bile ducts—lipomatosis and lipoidosis in the kidneys.

Owing to the understanding that it is the pure cholesterol stone which lies the longest in the bladder, an assumption should not be out of place that by reason of the constant irritation which goes on it has every possibility of giving rise to a cancerous degeneration of the mucous membrane of the gallbladder. Furthermore, when cancer is found situated where there has been the most irritation in walking and standing positions, i. e., the fundus, it would seem most likely that cancer of the bile ducts and gallbladder is secondary to stone and that the explanation of the absolute correlation to pure cholesterol stone is to be sought here.

That correlation exists between lipomatosis and gallstones is already proved and in various ways, as also is the assumption that this correlation should refer to the cholesterol stones mentioned by Naunyn,³ Aschoff⁹ and others. This investigation not only indicates the existence of decided correlation between lipomatosis and cholesterol stones, but also points out the nonexistence of a correlation between lipomatosis and pigment stones (see table 6, "All Stones"). How is this correlation to be interpreted? There are statements in the literature (McNee, Bacmeister and Landau) to the effect that a food rich in cholesterol might to some extent increase the percentage of cholesterol in the bile by cholesteremia¹⁰ and, further, that such an increase is likely to bring in its train cholesterol or pigment-calcium stones which may be in the bladder already or eventually precipitate cholesterol crystals, thereby constituting the first predisposition toward a primary crystalline cholesterol stone.^{9a} Should this assumption be correct, one has an obvious expla-

9. (a) Aschoff, L.: Von den Bedingungen der Gallensteinbildungen, *Deutsche med. Wchnschr.* 52:1755 and 1799, 1926. (b) Aschoff, L., and Bacmeister, A.: *Die Cholelithiasis*, Jena, Gustav Fischer, 1909.

10. Boysen,² p. 793.

nation of the connection existing between lipomatosis and pure cholesterol stones.

3. Pigment calculi were found in association with calcifications of various kinds, especially tuberculous calcification and perhaps healed tuberculosis.

In considering the correlation of these diseases, or rather, these conditions with gallstones (table 5), one comes to the conclusion that the correlation was due to the tendency toward calcification in pathologic processes which existed previous to these conditions. When it is seen that the correlation refers to the calcareous stones, it is not difficult to assume that in connection with these conditions the percentage of calcium in the bile increases and a tendency to calcification of the foreign substances found there arises. This is only an assumption, however. It has been proved experimentally that the calcium in the bile does not increase if the percentage of calcium in food is augmented. This cannot be said in any way to interfere with the foregoing hypothesis, as in the present case reference is made to the metabolism of calcium in connection with pathologic conditions.

4. The mixed pigment-cholesterol-calcium stones were found primarily in association with chronic cholecystitis.

In a case of prolonged chronic cholecystitis, increased quantities of albumin appear in the bile, and considering that albumin is one of the most important coagulating factors in connection with the formation of stone, the possibilities of a combination of the various substances forming a pigment-cholesterol-calcium stone are not far to seek.

SUMMARY

Gallstones, a common complaint, occurs in Stockholm in approximately one tenth of the inhabitants. The incidence in Sweden varies, however, according to the location. Stones appear to occur more frequently in rich and fertile districts and are of rarer occurrence in poorer and more barren areas. The incidence varies also according to time and seems to be less frequent during years of famine and the years immediately following than in times of plenty.

Only a fractional number of the patients (in this case, one fourth) have clinical symptoms of gallstones. But making reservation for miscalculations, due to the method of investigation, concerning what one would wish to consider the conspicuous results of one's investigation, it would seem that as soon as symptoms in the form of "typical painful attacks" appear, the risk of later complications, such as cholecystitis and cholangitis, is very great, especially in the case of repeated attacks.

Certain diseases and pathologic changes show a decided correlation with gallstones. This correlation refers only to certain types of stones;

consequently, cirrhosis and especially hemosiderosis of the liver, i. e., processes which accompany the accumulation of pigment in the liver, show an actual correlation with pigment stones, especially those which are of the pure type. Lipomatosis shows an actual correlation with pure cholesterol stones; calcification, especially tuberculous calcification, i. e., when there is a tendency to calcification in pathologic processes, shows an actual correlation with pigment calculi; and, lastly, cholecystitis—especially the chronic form, i. e., a process which augments the albumin of the bile, its most important coagulating factor—shows an actual correlation with the mixed pigment-cholesterol-calcium stones.

CHONDROMATOSIS OF THE JOINTS

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Despite the great number of articles on chondromatosis of the joints which have appeared since Reichel's publication in 1900, the condition has remained an interesting problem which by no means is entirely solved. From a review of the literature one gets the impression that the diagnosis, which is very simple when the condition is outspoken, is made too often and that many conditions which belong to the group of hypertrophic arthritis are diagnosed as chondromatosis because of the presence of a great number of joint bodies. Chondromatosis of the joints is a rare condition. Only three cases were found in the extremely rich material of the orthopedic department of the State University of Iowa. A diagnosis of chondromatosis was made many times, but the diagnosis did not withstand a more critical analysis. Three cases are reported here which were interesting from a clinical and a pathologic point of view.

REPORT OF CASES

CASE 1.—A man aged 29 complained of limitation of motion in the left shoulder. He stated that nine years prior to admission to the hospital he was thrown from a horse. Shortly afterward his left arm began to atrophy, and he could lift it only a little. Within a year the power gradually returned, so that he was able to work again, but occasional pain and limitation of motion remained.

Physical examination showed that the left shoulder and arm were slightly atrophic. Motion was limited to 45 degrees of abduction, 40 degrees of external rotation and 45 degrees of flexion. The last degrees of motion were painful and seemed to be checked by a bony obstacle.

A roentgenogram (fig. 1A) showed that the inferior two thirds of the left shoulder was filled with numerous calcified round bodies, most of which were the size of a pea. The uniformity and the dense arrangement of the bodies gave a grapelike appearance. Two greater foci could be made out, a larger one situated more medially and a smaller one laterally, apparently along the long head of the biceps muscle in the intertubercular groove. The head of the humerus was misshapen and flattened, and there was some erosion of the bony joint surface. The joint space was slightly widened.

The diagnosis of chondromatosis of the shoulder was made, and an open operation was performed. The joint capsule was found to be thickened. The entire joint space was filled with numerous small, free cartilaginous masses, ranging from 1 mm. to 1 cm. in diameter; some were smooth and shiny, and others were mulberry shaped. The head of the humerus and the glenoid fossa were covered with thin blue cartilage. All bodies which could be found, about 160, were removed, and the capsule was closed again.

The patient was reexamined one year and seven years after operation. The shoulder was well movable. There were some crepitation in the joint and some

atrophy of the deltoid muscle, but the patient had almost full use of the extremity and was well pleased with the result.

Of interest was the roentgenographic study. The picture (fig. 1 *B*) taken immediately after operation showed the number of calcified bodies to be greatly reduced. The lateral focus had been removed entirely, and medially there was still a good number of bodies present. A roentgenogram (fig. 1 *C*) made one year after operation showed that the number of bodies had further decreased. There was practically only one larger body present in the inferior portion of the joint and two smaller ones in the upper portion, which were not so densely calcified and apparently lay between the ends of the joint. The head of the humerus was markedly deformed and showed an uneven joint surface.

The histologic study revealed data of considerable theoretical significance. For this reason, an extensive pathologic report is given. A tag of synovial tissue (fig. 2) was examined which contained four more or less spherical cartilaginous

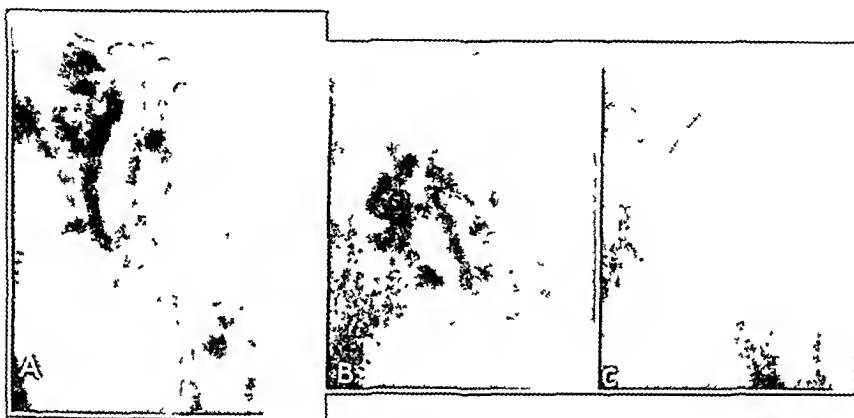


Fig. 1 (case 1).—Chondromatosis of the shoulder joint. *A* shows numerous calcified joint bodies filling the joint cavity and extending along the long head of the biceps in the intertubercular groove; *B*, the joint bodies remaining after operation; *C*, spontaneous resorption of joint bodies one year after operation. There is considerable deformity of the head of the humerus.

bodies. The density of the fibrous tissue of the tag varied, and there were a good many blood vessels. Synovial endothelium covered the smoother surfaces.

In the fibrous tissue there had occurred infiltration with a homogeneous reddish substance (fig. 3) which separated the collagenous fibers widely but did not interfere with their visualization. The cells, too, lay at greater distances from each other and assumed a spindle or stellate shape. In certain areas they had disappeared almost entirely, and then only a pinkish ground substance traversed by some fibers was to be seen. This represented the beginning of cartilaginous transformation of fibrous tissue.

It was of interest to see that close to an area which had already become impregnated by ground substance, the connective tissue was similar to embryonal mesenchymatous tissue and contained small spindle-shaped and starlike cells, the fibrous meshwork being spread apart by edema. It is possible that the edema and the embryonal character of the connective tissue were preceding even the process of impregnation by cartilaginous ground substance.

In certain places and at the same time, but apparently independently of the process of cartilagification, bone formation had taken place in the synovial fibrous tissue. The process of ossification was a primitive one, having as its basis fibrous tissue which became infiltrated by osteoid substance with the appearance of a greater number of cells, which in turn took over further bone apposition in form of osteoblasts. Calcification of the osteoid substance followed quickly.

Owing to the considerable proliferation of the young cartilaginous tissue, the focus had increased in size and showed, as it is characteristic for joint bodies, a certain tendency for concentric structure (fig. 4). This was seen especially well when there was calcification of the cartilage. Some of the small bodies were calcified almost in their entirety with dense precipitation of lime salts around the cartilaginous cells. The latter frequently disintegrated and even completely dis-

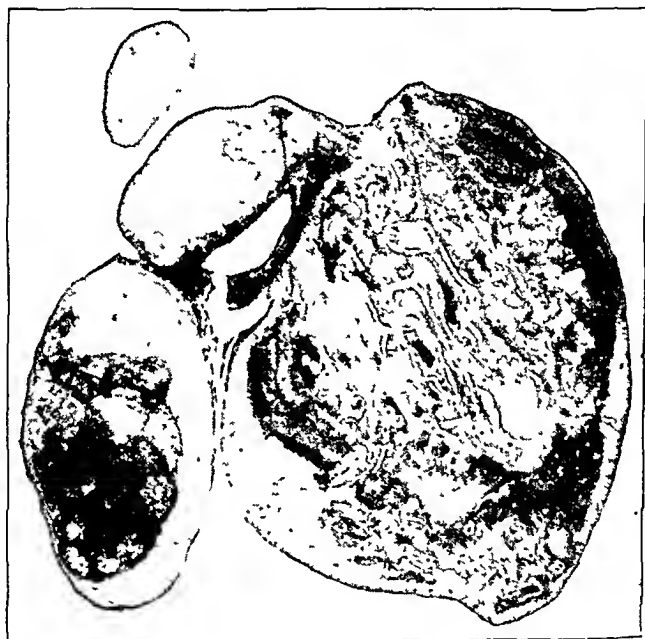


Fig. 2 (case 1).—Low power picture of a synovial tag containing four bodies, in part purely cartilaginous and in part osseous, with fibrous bone marrow. The bodies are united by strands of hyperemic synovial connective tissue.

appeared. When this occurred the calcification was more homogeneous, involving ground substance and cell groups evenly. If, however, the calcification was not associated with necrosis of cartilaginous cells, later a secondary process of cartilage resorption took place owing to reactivation of the cartilage cells (fig. 5). This means that the cartilage cells included in calcified ground substance remained for some time in an active stage of low vitality. Later, for some unknown reason, they regained activity and, similar to the formation of Weichselbaum's lacunae in the joint cartilage, only with the difference that the latter develop in noncalcified cartilage, maintained a resorptive process which led to widening of the cell cavities by chondroclasia. Thus there appeared wide and lacunar cavities, separated from each other by irregular septums of calcified cartilaginous tissue

and filled by cartilaginous cells, which under proliferation showed a backward development toward fibroblasts.

More evident and easier to understand was the process of calcification along the periphery of the calcified joint bodies, where synovial fibrous tissue was preserved in the form of perichondrium. The superficial layers of this perichondrium, more exposed to traumatization during motion of the joint, were rather dense, with parallel concentric structure of the fibers. The deeper layers, protected from



Fig. 3 (case 1).—Higher power photomicrograph than that in figure 2, showing the peripheral zone of one of the bodies. Diffuse impregnation of synovial fibrous tissue by primitive (eosinophilic) cartilaginous ground substance and rapid disappearance of cartilaginous cells are seen. Very cellular and well vascularized superficial layer of fibrous tissue is present—future perichondrium.

mechanical irritation, were loose and rich in cells and could be considered as a true cambium layer (figs. 4 and 5). This layer bordered on the calcified layer along a sharply lacunar line with mononucleated and multinucleated phagocytic elements in the lacunae. These cells were true chondroclasts, being derived from

the fibrocytes of the perichondrium and cambium layer. It could, however, also be seen that with this process of cartilage resorption, the cartilaginous cells up to now lying in calcified substance, as soon as they were freed changed to large fibrocytes, which participated in the composition of the cambium layer.

Blood vessels were not present over the lacunar area. It seemed that this process of decalcification was purely cellular or enzymatous and that a blood supply was not a prerequisite.

The largest of the joint bodies consisted of bony tissue to a considerable degree (fig. 2). The distribution of the different tissues was as follows: On the surface there was fibrous tissue in form of a perichondrium. Close to the surface there was noncalcified hyaline cartilage of not very high maturity. The cells were still spindle shaped, rarely spherical and without a tendency to group formation.

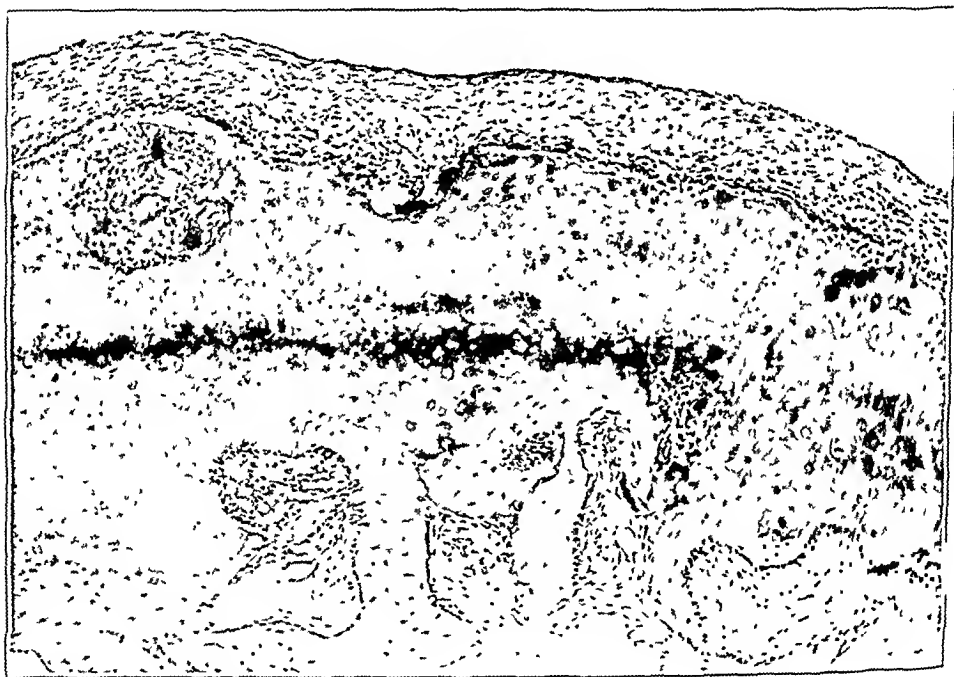


Fig. 4 (case 1).—Photomicrograph of the peripheral zone of a cartilaginous bony body, showing calcification of the superficial cartilaginous layer with definite concentric arrangement of increased zones of lime salt deposits; resorption of calcified cartilage from below and replacement by bony tissue; active osteoblastic bone apposition within the fibrous marrow spaces; resorption of calcified cartilage from above by multinucleated chondroclasts, and a fibrous tissue layer in the form of perichondrium on the surface.

As soon as calcification of the cartilage took place, the cells lay at greater distances from each other. They were more round and stood out more distinctly because of stronger calcification around the cells. The innermost portions of the body were made up of bony tissue. It was of interest to study the process of ossification.

The calcified cartilaginous tissue was often in intimate relation to the bony tissue. The most common form of osteogenesis was a primitive type of enchondral

ossification. Fibrous bone marrow with well vascularized processes invaded the calcified joint cartilage from below, which yielded under this vascular and chondroclastic resorption. On the lacunar surface of the calcified cartilage, bony tissue became apposed by osteoblasts, leading to the formation of primary spongy bone.

Enchondral ossification of this primitive type without any zone of cartilaginous proliferation was, however, not the only form of osteogenesis. It has already been mentioned that with synovial fibrous tissue as a basis, cartilaginous as



Fig. 5 (case 1).—Photomicrograph showing lacunar resorption of calcified cartilage by reactivation of the included cartilage cells. The freed cells form a part of the cambium layer of the perichondrium.

well as bony tissue may develop quite independently of each other at the same time in different places. The two tissues can merge, in which case a picture would result suggestive of direct metaplasia from cartilage into bony tissue. Such local connections of the two tissues are, however, not to be taken necessarily as genetic. They can be merely a topographic coincidence of the two tissues, which have developed independently in a common matrix of fibrous tissue.

As soon as bony trabeculae had formed, an active process of bone transformation could be observed. The irregular network of bony trabeculae was covered on its endosteal side by osteoblasts of almost epithelial connection, or, where bone absorption had taken place, with multinucleated osteoclasts in Howship's lacunae. With this process of bone transformation, the bone marrow also underwent changes. Fat cells appeared in the primarily well vascularized connective tissue, and one could see all the different stages from small lipoblasts with foamy protoplasm to large fat cells, which gradually occupied the entire marrow spaces.

The picture, in a general way, was that of rapid growth but also of rapid decline. The great amount of osteoclasts and chondroclasts made it easy to understand that joint bodies, as soon as calcification has taken place, may again disappear by cellular resorption. This fact explained also the peculiar finding that the synovial connective tissue between the cartilaginous bodies was extremely rich in



Fig. 6 (case 1).—Photomicrograph showing a strand of synovial tissue with many inclusions of small lacunar particles of calcified material (result of resorption of disintegrated calcified bodies) and a small island of mature hyaline cartilage attached to the synovia by fibrous tissue (appearing loose in the section).

small calcified fragments (fig. 6). They were lying included in the fibrous tissue without any reaction around them or were still undergoing disintegration by osteoclasts.

CASE 2—A man aged 25 complained of pain and stiffness of the left hip joint. He was in excellent health up to four months before admission to the hospital, when he was suddenly seized by a sharp pain in the left hip while planting a garden. As he stooped over he felt something pop in his left hip, and since he could not straighten out he had to stay for a while bent forward; then he went down on his knees and spread his legs. This relieved the sharp pain. From this time on, the left hip remained in an abducted position. The patient had to go to bed because of the pain. The condition was diagnosed as rheumatism by a doctor. Heat

relieved the pain somewhat, but the most comfortable position was one of marked abduction and flexion of the leg. He was under the treatment of a chiropractor without effect.

On physical examination, the patient appeared to be in good health. He walked with marked abduction contracture of the left leg and was scarcely able to put weight on this extremity. The left hip joint was kept in a position of 30 degrees of flexion and 40 degrees of abduction. There was tilting of the pelvis upward and backward to compensate for the contracture and atrophy of the thigh of 3 inches (7.6 cm.). The region of the hip joint was not swollen or especially tender, and there was no local heat. From the contracted position of the joint, further abduction and flexion motion was free. Other motions could not be carried out, and any attempt to do so was extremely painful.

The roentgenograms (fig. 7) revealed considerable bony atrophy around the hip joint. The left femur was held in abduction of about 40 degrees. The head of the femur was well shaped but appeared to be pushed out from the socket so



Fig. 7 (case 2).—Roentgenogram of the left hip joint in marked abduction contracture. The head of the femur is subluxated and pushed out off the socket by an accumulation of noncalcified joint bodies in the lower portion of the hip joint.

that the joint space in the lower half was about twice as wide as that on the right normal side. The tear figure of the acetabulum was well developed. There was some obliquity of the roof, and the fossa acetabuli was definitely larger and slightly deeper than on the right side. The joint space in the upper portion of the joint was of normal width. There were no signs of arthritic erosion.

No definite diagnosis could be made. A tuberculous lesion of the hip had to be considered because of the strongly positive reactions to the cutaneous tests, but the patient's general health was good, and there had been no loss of weight and no fever. The widening of the joint space in the lower half suggested some soft tissues pushing the head gradually out, and an intra-articular new growth was considered. To arrive at a more conclusive diagnosis, biopsy was indicated.

The left hip joint was exposed through a Smith-Petersen incision. The joint capsule seemed to be thickened slightly on the anterior side, but this was considered as due to the flexion position of the joint, leading to some redundancy of the anterior joint capsule. The joint capsule was incised in the form of an H,

the cross-beam of which represented a longitudinal incision along the iliofemoral ligament, while one of the vertical portions of the H ran along the rim of the acetabulum, and the other around the neck of the femur. As soon as the capsule was incised, rather thick clear yellow synovial fluid escaped, carrying with it a few small cartilaginous bodies. More could be seen with further exposure of the joint. The bodies were purely cartilaginous and soft and varied in size from that of the head of a pin to that of a small pea. They were rarely truly spherical. When they were a little larger, they slightly resembled mulberries because of the presence of many small round prominences. The synovial membrane, as far as it could be seen from the incision, appeared to be of normal thickness. It was slightly hyperemic and extended from the neck of the femur toward the margin of the joint surface, here eroding, in an uneven way, the peripheral portions of the joint cartilage. The head of the femur was dislocated in the wound. The ligamentum teres was cut at its insertion to the fovea capitis. A peculiar picture presented itself at this area: The synovial cover of the fovea, extending then along the ligamentum teres, showed numerous small islands of cartilaginous tissue. The joint cartilage of the femur was slightly thinned out over the anterior portion, which had been out of contact with the acetabulum and probably under some pressure from the side of the joint capsule. The cartilage over this area was without its normal glistening appearance, thus revealing the first stage of degeneration. The insertion of the ligamentum teres together with the neighboring portions of the head were removed radically.

After complete dislocation of the head, the acetabulum was inspected. A startling picture was encountered. The entire acetabular cavity was densely filled with a great number of cartilaginous bodies of variable size, almost all of which were free. There was no doubt that by the accumulation of these cartilaginous bodies the head of the femur had gradually been pushed out from the socket. Body for body was carefully removed until the ground of the acetabulum was visible. It showed exactly the same changes in the synovial tissue as were seen in the fovea capitis, with the exception that they were much more extensive. The acetabular cavity was thoroughly curetted until one could be sure that all the diseased portions were radically removed. It was tiresome to remove all the tiny joint bodies, because a great many were hidden in the different reflexions of the capsule. Three hundred and ninety-five free bodies were counted; the smallest ones were still attached to the synovial membrane, like corals to a reef. The head of the femur was then reduced, and the wound was closed in layers.

Unfortunately, a postoperative streptococcic infection developed, which necessitated wide and multiple drainage of the hip joint. The patient is now recovering from the infection, but it is doubtful how much useful motion he will preserve in the hip.

The histologic picture resembled in many respects that seen in case 1, but the process was not quite as advanced. Here too one could notice that the first stages in the formation of the cartilaginous bodies consisted in the appearance of a cartilaginous ground substance between the cells and the fibers of the synovial connective tissue. In this case, however, the ground substance had a clearly basophilic character from the beginning; it was pale blue even in those areas where the cells showed still more resemblance to fibrocytes than to cartilaginous cells and where, because of the incomplete impregnation of the collagenous fibers, the newly formed cartilage had to be classified as a more primitive fibrous cartilage.

Within this fibrous cartilage, certainly at the same time and in different places, there was marked proliferation of certain cells which more and more

assumed the appearance of mature cartilaginous cells and showed a definite tendency to group formation. The different cartilaginous centers, of more mature structure and showing very active proliferation, expanded in centrifugal direction. The cellular activity was evidently the main factor in promoting the growth, even the increment of the ground substance, for which, as one could see over and over again, mainly the necrosis and disintegration of the cell groups and their transformation to ground substance were primarily responsible. The necrosis of cartilaginous cells occurred apparently very rapidly, and the same was true with their assimilation to hyaline ground substance. The centrifugal direction of the growth of the cartilaginous foci or bodies could easily be recognized also from fields of degeneration in the oldest, i. e., central areas of greater cell growth, where the so characteristic form of asbestos degeneration of cartilage was a frequent finding.

It was also interesting to observe that the foci of hyaline cartilage, which resulted from localized increased proliferative power of certain cells of the primary fibrous cartilage, extended later within and toward the mother soil. The foci of hyaline cartilage were then found, with sharply outlined convex globules, bordering either on the primary fibrous cartilage or on the synovial fibrous tissue, thus compressing and gradually replacing the mother tissue.

All the free bodies were made up only of hyaline cartilage. Calcification was an extremely rare finding. Beginning deposition of lime salts was seen in only a few places. It was arranged in wreathlike fashion around the cell groups and from here gradually extended into the septums of hyaline ground substance. Bone formation did not occur in any of the bodies that were examined.

CASE 3.—A man aged 52 complained of pain in the left hip. Clinical symptoms started more than two years before admission to the hospital, when he slipped on a greasy floor and fell. He hobbled about and had to go home in a car. He was in and out of bed during a period of about three weeks; then he tried to work for two days but was unable to do so. The hip and back were strapped. He was kept in a hospital, where traction was applied for six days; he then wore a plaster cast for four weeks. After that time he was worse than before. The hip and knee joints stiffened.

On physical examination the patient appeared to be in good health. The left hip joint was kept in a position of 25 degrees of flexion, 10 degrees of abduction and 30 degrees of external rotation. There was only 25 degrees of free flexion motion.

Roentgenograms taken at different times before the patient's admission to the hospital revealed the following conditions:

Four weeks after the onset of the symptoms (fig. 8A) a calcified joint body the size of a bean was present at the inferior aspect of the proximal end of the femur, being separated from the neck by a narrow zone of 1 mm. One pole of the body was sticking in a small troughlike impression at the joint margin of the head of the femur. The other pole of the body was apparently in connection with another smaller body of lesser density, which was partially hidden by the cortex of the neck. There were only mild hypertrophic arthritic changes of the left hip joint, those on the right being a little more marked, with exostoses at the inferior part of the acetabulum.

Ten months after the onset (fig. 8B) the two bodies at the inferior aspect of the head of the femur were still present, practically unchanged. A third body of the same structure had appeared, inferior to the margin of the joint. The joint space was well preserved.

Thirteen months after the onset the three bodies had apparently united and formed a sharply outlined, not densely calcified body in the inferior portion of the joint.

Two years after the onset (fig. 8 *C*) the calcified mass in the hip joint had increased remarkably in size and was forming a tumor which filled the entire lateral compartment of the joint, extending laterally to the greater trochanter.

At the time of admission the picture was the same as previously described.

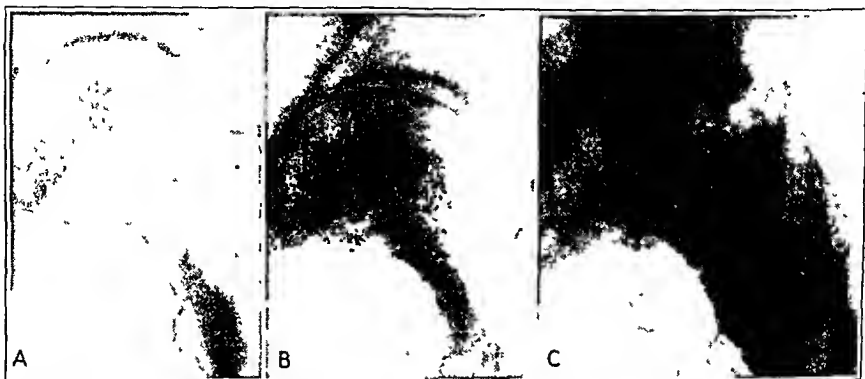


Fig. 8 (case 3).—Pictures taken at intervals showing the development of the big cartilaginous-bony intra-articular mass. There are mild hypertrophic arthritic changes of the hip joint.

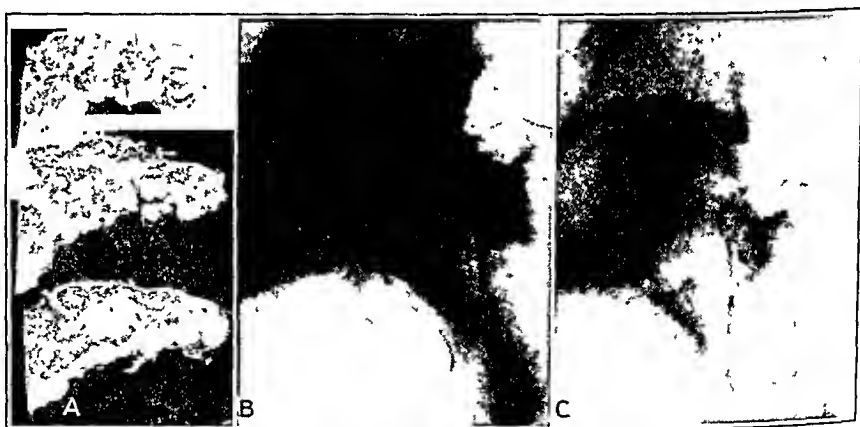


Fig. 9 (case 3).—Pictures taken after incomplete surgical removal of the intra-articular tumor. There was ossification above the hip joint after stripping of the periosteum. *A* shows three slices through the tumor. The lobulated surface is covered by mature hyaline cartilage and the central bony areas.

The whole series of roentgenograms strongly suggested chondromatosis of the hip joint as a diagnosis. Removal of the bodies was indicated.

The hip joint was opened by an anterolateral incision. There was a large mass of cartilaginous-bony consistency, lobulated (fig. 8) and covering the lateral portion of the neck anteriorly and inferiorly. It measured about 5 by 4 by 2 inches (12.7 by 10 by 5 cm.). It was entirely intracapsular and was not attached

firmly in any place, and could be removed relatively easily. The capsule was thick, but the synovial membrane did not show more marked pathologic changes. The joint cartilage of the head of the femur appeared to be normal. There was full range of motion as soon as the tumor was removed. After the operation, with the patient under general anesthesia, two manipulations were performed to increase the amount of motion. Half a year later he felt much improved and had a good range of motion. The leg was, however, kept in considerable external rotation.

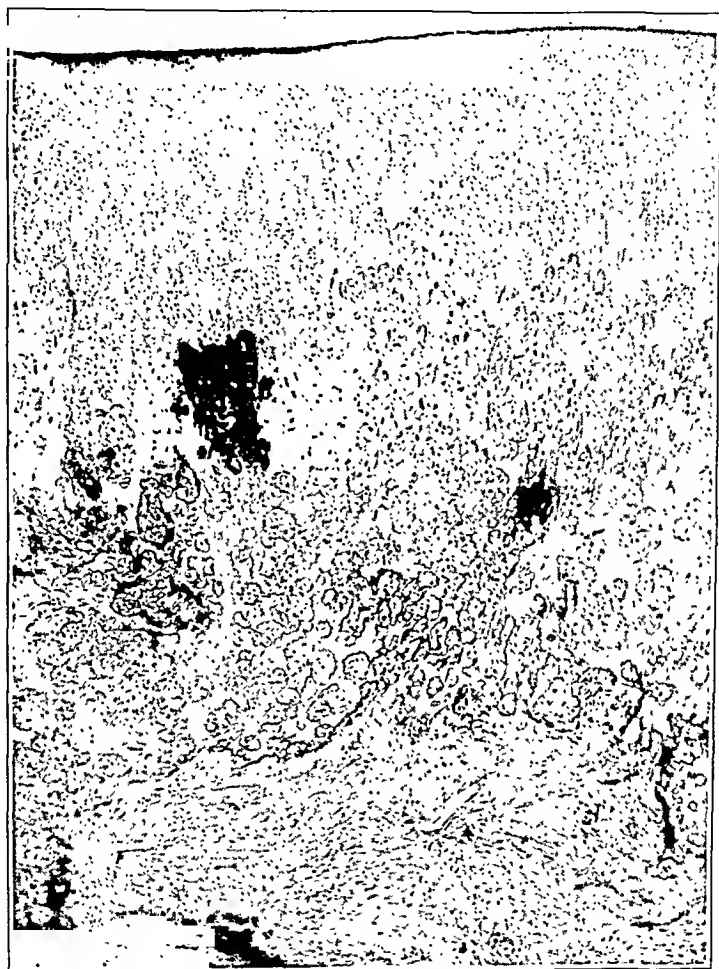


Fig. 10 (case 3).—Photomicrograph of the cartilaginous cover with proliferation of the deeper cellular layers, irregular calcification of ground substance in the deeper strata, especially around the cell groups, and vascular resorption of cartilage, not followed by ossification.

Roentgenograms taken half a year after operation (fig. 9B) revealed that a part of the calcified tumor had remained in the inferior compartment of the joint, where it had led to definite pressure atrophy of the neck of the femur. There was irregular ossification of the superior aspect of the neck, a result of the stripping of periosteum at the time of operation.

The patient was seen two years after the operation. He was complaining of weakness and pain of the left lower extremity, which was kept in 30 degrees of external rotation and 40 degrees of flexion contracture. There was flexion of 45 degrees, but all other movements were abolished. He walked with a marked limp.

Roentgenograms (fig. 9 *B*) showed that the portion of the tumor which had remained in the joint had apparently fused to the inferior surface of the neck. It was definitely smaller and had more regular structure. It was most likely that the cartilaginous mass had become ossified and that the whole process had come to a standstill.

The pathologic examination of many different portions of the tumor showed a picture which resembled closely that of osteochondroma. The densely lobulated

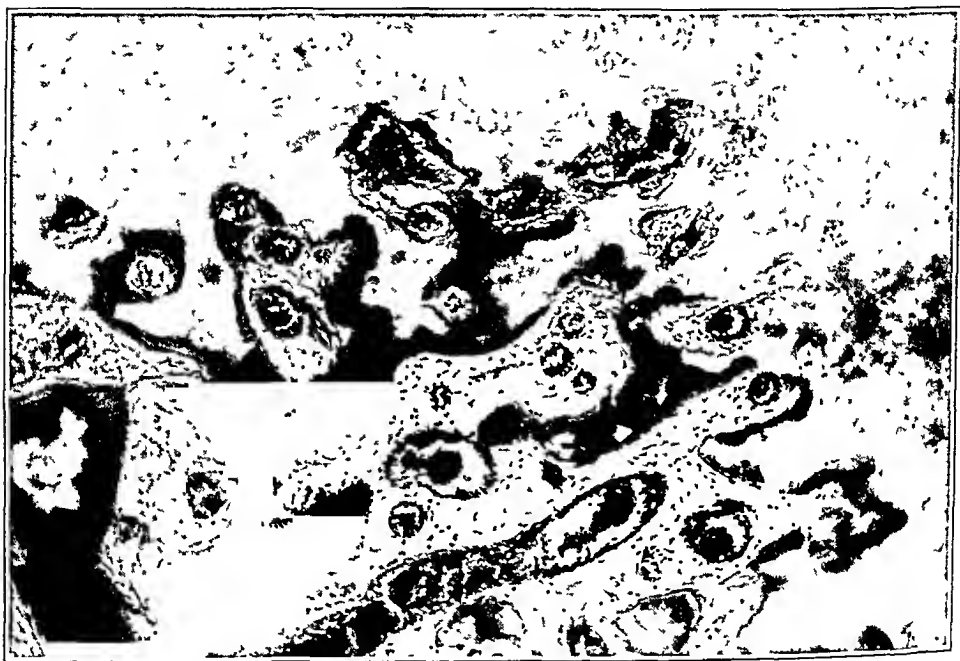


Fig. 11 (case 3).—Photomicrograph of enchondral ossification at the lower surface of the cartilaginous cover. There is no column formation of proliferative cartilage. An irregular zone of calcification and pronounced vascular resorption with osteoblastic bone apposition are seen.

mass had a relatively thick cover of hyaline cartilaginous tissue, which showed considerable proliferative activity of the deeper cellular layers, whereas the more superficial layers with their small and flattened cells gradually blended into fibrous tissue, which could be considered as perichondrium. The fibrous tissue between the lobules was relatively dense and very vascular—a certain sign that the tumor had been attached to its adjoining area, i. e., either to the joint capsule or to the neck of the femur. The cartilaginous cover of the tumor showed enchondral ossification from below, which in some places was quite active. The bony tissue was coarse and in rapid process of structural transformation. The narrow spaces contained hyperemic and edematous loose fibrous bone marrow.

COMMENT

I do not intend to discuss here in a general way the clinical and roentgenographic picture of chondromatosis of the joints. It has been done before, and a number of excellent articles are available (Rostock,¹ Henderson and Jones,² Eden³ and Janker⁴).

From the clinical and the anatomic study of these three cases, I should like to make a few remarks concerning the pathogenesis of chondromatosis of the joints. (I prefer the term chondromatosis to osteochondromatosis, because, as case 2 showed definitely, the lesion may be advanced and still there may be no new bone formation.) Since Lexer's⁵ article in 1907, the idea seems generally accepted that chondromatosis is derived from a blastomatous growth from many dispersed particles of cartilaginous tissue lying in the synovial membrane since its embryonal development. Although Lexer was able to explain a good many of the features of chondromatosis with his theory of embryonal germ dispersion, I do not think that he and his followers are correct. The histologic picture in the beginning stages of chondromatosis speak against considering chondromatosis as a blastoma. If Lexer were right, one would expect to find within the synovial connective tissue small centers of hyaline cartilage, by autonomous proliferation of which small chondromas develop. Later stages of chondromatosis may suggest such an origin. However, if one concentrates on the first histologic changes, one misses entirely the dispersed cartilaginous germs and finds a picture of impregnation of synovial connective tissue with cartilaginous ground substance. The cells included preserve for a while their character of fibrocytes, and the tissue resulting is therefore fibrous cartilage. As far as the cartilage growth is concerned, the process is rather diffuse from the start and not, as one would expect from Lexer's theory, circumscribed. Later, within the primary fibrous cartilage a more circumscribed proliferation of certain cells takes place. The cells gradually assume the typical picture of cartilage cells and assemble in groups, and larger areas of hyaline ground substance result chiefly from disintegration and homogenization of cartilaginous cells. Such centers of increased cellular activity gradually suppress and replace the fibrous cartilage from which they developed. At such a stage one could be induced to accept Lexer's idea.

Bone formation occurs secondarily in all the different ways, as ossification may be seen also in other places; enchondral ossification is fre-

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1. Rostock, P.: *Beitr. z. klin. Chir.* **144**:58, 1928.
 2. Henderson, M. S., and Jones, H. T.: *J. Bone & Joint Surg.* **5**:400, 1923.
 3. Eden, R.: *Arch. f. klin. Chir.* **104**:277, 1914.
 4. Janker, R.: *Deutsche Ztschr. f. Chir.* **211**:135, 1928.
 5. Lexer, E.: *Deutsche Ztschr. f. Chir.* **88**:311, 1907.

quent, but more primitive forms suggesting metaplasia of cartilaginous into bony tissue are not rare.

The histologic picture of chondromatosis is essentially similar to that of myositis ossificans, in which cartilaginous and bony tissue develop in exactly the same way within the connective tissue of the skeletal musculature. Myositis ossificans has also been considered by some as a blastoma and by others as an inflammatory process (Reichel,⁶ the first to describe chondromatosis, considered it also a contagious agent), which, infecting the synovia and spreading within the joint is thus leading to the picture of diffuse chondromatosis). There seems to be now more and more agreement (Macrycostas⁷ and von Meyenburg⁸) concerning myositis ossificans, the theory being that it is neither a tumor nor an inflammatory process. Against the theory that it is a tumor are the facts that myositis ossificans, even if left unhindered, does not grow toward a spherical shape, its growth is not unlimited, it frequently comes to a spontaneous standstill and it may even completely disappear if the causative (mechanic-traumatic) factor is removed. One is therefore justified in considering myositis ossificans as a localized metaplastic hyperplasia of the connective tissue of the skeletal musculature. It is metaplastic, however, mainly in the sense that there is indirect metaplasia with simultaneous development of cartilaginous and osseous tissue in the common matrix of connective tissue.

I feel that the same is true with chondromatosis of the joints. Chondromatosis is not a blastoma of the joint capsule; the marked proliferative activity is not sufficient reason to classify the growth as a true tumor. It is just a hyperplastic process of synovial tissue in which the close embryonal relation to cartilaginous tissue becomes manifest. The external differences between chondromatosis and myositis are due mainly to the different localization of the processes. In myositis ossificans, the process is localized in the connective tissue of the musculature; in chondromatosis, in the synovial membrane, which undergoes the metaplastic changes, and, owing to the phylogenetic and ontogenetic relation of synovia to cartilage, there is greater tendency to cartilage formation in chondromatosis.

As myositis ossificans chondromatosis may appear as a localized and as a progressive or diffuse lesion, the entire joint capsule may show the hyperplastic changes or only a relatively small part of it (case 2). The process may remain limited to the synovial tissue (this is the rule), or it may expand, break through the fibrous joint capsule like a malign-

6. Reichel: *Arch. f. klin. Chir.*, 1900, vol. 61.

7. Macrycostas: *Arch. f. klin. Chir.* 158:584, 1930.

8. von Meyenburg, H., in Henke, F., and Lubarsch, O.: *Handbuch der speziellen pathologischen Anatomie und Histologie*, Berlin, Julius Springer, 1929, vol. 9, p. 391.

nant growth and involve also the connective tissue of the surrounding musculature (this is the rare exception illustrated by Lexer's case). These differences most likely depend only on the degree of differentiation the mesenchymatous tissue has taken in the neighborhood of the skeleton. If the genotypic potency of the simple fibrocyte to produce supporting substances of any type is not too latent, then any of the connective tissue of the body may produce cartilage or bony tissue by a hyperplastic metaplastic process, which is more extensive the closer it is situated to the skeleton.

In a number of instances of chondromatosis of the joints there is a gradual decline or even a complete disappearance of the joint bodies, as in cases of myositis ossificans. Cases 1 and 3 are good examples, and other cases have been reported in the literature. In cases 1 and 3, the operation did not succeed in removing completely the cartilaginous and bony masses; the roentgenograms taken after the operation showed a number of bodies remaining. Nevertheless, the roentgenographic follow-up study in both cases revealed a spontaneous diminution in the number and size of the remaining bodies. This shows clearly that the hyperplastic process exhausts itself gradually and the cartilaginous cells cease to proliferate, whereas ossification continues until all the cartilage has been removed—a picture similar to the physiologic process of enchondral ossification with the final disappearance of the epiphysal plates. The bony tissue may, later, also become completely resorbed by cellular (osteoclastic) activity. Such a fact speaks strongly against the possibility of the process being a tumor.

The histologic picture in case 1, with the numerous small lacunar particles of calcified material lying in the synovial fibrous tissue, gave a vivid impression of the rapid disappearance of calcified joint bodies by cellular activity. It could be also considered that some of the joint bodies became crushed during motion of the joint, and smaller fragments floated for some time in the synovial fluid. Later, they may have settled in small pockets or at the sites of reflexion of the synovial membrane and gradually become included and resorbed in the synovial layers. Similar pictures can be observed in any case of intra-articular fracture.

From this analogy between myositis ossificans and chondromatosis, one could conclude that in a number of cases of more clearcut traumatic origin the hyperplastic activity of the synovial connective tissue could be overcome by the seclusion of secondary traumatic irritating factors under immobilization and rest in the same way as it is so frequently with traumatic myositis in the region of the elbow. Further observation will be necessary to settle this question.

As far as the etiology of chondromatosis is concerned, it remains just as obscure as that of myositis ossificans. The cases reported here do not permit any new conclusion in this respect.

Unusual and worth the emphasis is case 2, in which the diagnosis could not be made before the exploratory operation. Despite the presence of 395 free joint bodies, calcification and ossification had not yet occurred in sufficient strength to cast a shadow in the roentgenogram. The head of the femur has been partially pushed out from the socket, and the joint was locked in abduction and flexion. This is the only case of advanced chondromatosis in which a typical roentgenographic picture was not obtained. None of the cases reported in the literature was of similar character.

The condition in case 3, which is somewhat unusual because of the relatively high age of the patient (50), started apparently multicentrically, probably in some hypertrophied tags of synovial tissue, and most likely on a traumatic basis. Later the different centers merged and formed one large mass of cartilaginous-bony tissue, which histologically showed the most mature differentiation, resembling closely the structure of a true osteochondroma.

SUMMARY

On the basis of material in three cases, which has been carefully studied clinically, roentgenographically and pathologically, the idea is expressed that chondromatosis of joints does not represent a blastomatous change of the synovial membrane. The process is similar to that of myositis ossificans—a metaplastic hyperplasia of connective tissue. The close embryonal relation of synovia to cartilage explains the prevalence of cartilaginous tissue in chondromatosis. Spontaneous resorption of calcified bodies speaks in favor of a hyperplastic process also from a clinical point of view.

USE OF HOMOLOGOUS BONE GRAFTS IN CASES OF OSTEOPENESIS IMPERFECTA

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Fractures in cases of osteopenesis imperfecta usually heal without difficulty, but at times, after repeated fractures at the same site, union is either by fibrous tissue or by a soft osteoid tissue. Patients with ununited fractures or with severe deformities of the bones of the lower extremities, some of whom are unable to walk, are seen not uncommonly. In such cases, both as a result of the basic pathologic condition and from atrophy of disuse, the bones are very small and weak, making weight bearing, even with braces, impracticable.

A situation of this sort, which occurred in an 11 year old girl with severely deformed, ununited femurs, who never had walked, was the reason for my experimenting with homologous bone grafts from the tibias of the patient's mother in an attempt to correct the deformities, bring about union in the femurs, and, at the same time, strengthen them sufficiently to permit the child to walk. It was hoped that the stimulus of weight bearing might lead to further increase in the diameter and strength of the femurs, which could well be compared with clay pipe stems in size and brittleness. The success of the grafts in this case encouraged the use of the procedure in three other patients. In all, eight bones were operated on in four patients. The first operation was done on June 23, 1926, and the last on Sept. 19, 1935. With the exception of the last operation, which was done so recently that the result cannot be determined, the average time that has elapsed since each procedure is more than five years. Three of the patients were girls, aged 9, 9 and 10 years at the time of operation, and one was a boy, aged 13. Three femurs, four tibias and one humerus were operated on.

Onlay grafts from the donors' tibias were used in each case. In four operations one large graft was used, and in the other four two or more smaller grafts were employed. The periosteum was elevated from the bone over the area to which the graft was applied, and the latter was secured by several sutures of kangaroo tendon or chromic catgut, passed around the bone beneath the periosteum and around the graft. The grafts were used without periosteum and consisted of the full thickness of the cortex together with a layer of cancellous medullary bone.

When a pseudarthrosis existed, this area was excised. In cases of severe deformity two osteotomies were done in order to secure better correction and alinement, and the grafts were made to extend beyond both ends of the intermediate fragment.

The two femurs of the first patient were immobilized by means of the Taylor traction hip splint, designed for the treatment of tuberculosis of the hip. Although the result was satisfactory, in all of the subsequent cases the extremity was immobilized in a plaster cast. After seven operations the graft united to and became amalgamated with the bone to which it was attached, and firm union took place at the site of the fracture or the osteotomy. In some cases, however, union was slow and became strong only after several months. In all the cases the bones hypertrophied after the application of the graft, and in three the increase in size was very substantial. All four patients were able to walk after operation, although two were obliged to use crutches or braces. One femur and one tibia in the same patient fractured two and five years subsequent to the application of the grafts. The graft which was applied to a humerus had united lightly at the end of nine weeks, but the final result is still to be determined.

In three cases the bone was obtained from one of the parents and in the fourth from an unrelated donor. Two of the donors, both parents, had the same blood groupings as the patients. The remaining two, one parent and the unrelated donor, were of different blood groups. This did not appear to affect the result, and on theoretical grounds it should not, since it is believed that the bone graft acts simply as a scaffolding for new bone to grow on and that it also affords a supply of calcium. In two instances enough bone for two operations was removed from the donor. The excess was placed in a large sterile test tube and refrigerated until the second operation several weeks later. The bone was then placed in an autoclave before it was used. The results with these grafts were as satisfactory as with fresh ones.

The calcium, phosphorus and phosphatase contents of the blood were within normal limits in all four patients, as has been found in other patients with this condition. The mother of one patient had had osteogenesis imperfecta during childhood. There was no familial history in the other cases.

SUMMARY AND CONCLUSIONS

1. Four patients with ununited fractures and severe deformities of the bones of the lower extremities which completely prevented or seriously interfered with walking and with one deformed humerus with recurring fractures were treated with onlay bone grafts from the tibias of donors, after correction of the deformities.

2. In the seven operations on the lower extremities the grafts united, and the resulting correction of the deformities and hypertrophy of the bones enabled the patients to walk. The result of a similar operation on a humerus cannot yet be determined.

3. It is believed that a homologous bone graft can be used to advantage in such cases or in any case in which a bone graft is indicated and in which an autogenous graft cannot be obtained.

REPORT OF CASES

CASE 1.—M. V., a white girl aged 8 months was admitted to the New York Orthopaedic Dispensary and Hospital on Feb. 27, 1917. She was said to have been born with a fracture of each leg. Subsequently she fractured her right arm, which



Fig. 1.—Ununited fracture of both femurs in a patient 11 years of age. The patient never had walked.

united. On her admission there was a fracture of the right femur. This was treated with a plaster spica, and union occurred. In September 1917 she sustained a fracture in the upper third of the right femur. She was admitted to the ward for reduction of a fracture of the left femur in December 1917. A marked anterior and lateral bowing at the junction of the middle and the upper third of the left femur was corrected by manipulation in August 1918. Braces were subsequently applied. A fracture occurred at the junction of the upper and the middle third of the right femur in November 1924.

The patient was readmitted to the hospital on April 14, 1926, at the age of 9. She was short, with a large cranium and blue scleras. There was marked angular deformity at the site of ununited fractures at the junction of the upper and the middle third of the shaft of each femur. The child had never walked. By means of a Taylor traction hip splint the angle of deformity of the left femur was reduced

from 90 to 30 degrees, and a corresponding correction was obtained on the right side. On June 23 an open reduction of the fracture of the right femur and application of bone graft were done. The shaft of the femur was not more than 1.5 cm. in diameter, and the bone was extremely brittle. Three centimeters of bone was resected, including the site of the fracture and the fibrous tissue joining the ends of the fragments. In exposing the upper fragment, it was fractured about 4 cm. from its end, leaving a loose intermediate piece of bone. A large full thickness graft, about 3 by 12 cm., from the tibia of the patient's mother was then secured to the upper, lower and intermediate fragments with four sutures of kangaroo tendon. A Taylor traction hip splint was applied. Union of the graft to the femur took place gradually, being fairly firm in about five months.



Fig. 2.—Application of a graft from the mother's tibia to the right femur after resection of an area of pseudarthrosis; anteroposterior view.

On Feb. 15, 1928, the site of fracture of the left femur was exposed, and a wedge of bone, including the fibrous pseudarthrosis, was removed. A large tibial graft, 3 by 10 cm., from the mother's tibia was secured to the upper and lower fragments with four kangaroo tendon sutures. A Taylor traction hip splint was applied to the extremity. Union between the graft and the femur was very slow but was sufficiently strong in October 1928 for the patient to walk for the first time, with the aid of braces. She was discharged from the hospital on November 15. She was last examined on Feb. 16, 1933, at which time the femurs were comparatively well developed and strong. She was walking without braces.

CASE 2.—E. F., a 2 year old girl, was brought to the outpatient department of the New York Orthopaedic Hospital on April 3, 1922, with active rickets and a

deformity of the left tibia due to an old fracture. The patient's mother and a sister had several fractures during childhood, and both have blue scleras. She continued to have numerous fractures of the lower extremities, resulting in increasing deformities. She was admitted to the hospital in March 1930, at the age of 10 years, for the correction of marked anterior bowing of the left tibia. There was an ununited fracture at the junction of the middle and the lower third. On April 14 osteoclasts were done, producing a fracture above the site of nonunion and further correction at the pseudarthrosis. On May 5 the tibia was exposed, and the fibrous tissue and eburnated bone were resected from the site of the fracture, and better alignment was secured. Two pieces of bone 6 inches (15 cm.) long, $\frac{1}{2}$ inch (1.3 cm.) wide and $\frac{1}{4}$ inch (0.6 cm.) thick, which were taken from the father's tibia, were tied on each side of the upper, lower and intermediate fragments with kangaroo tendon. The periosteum was sutured over the tibia, and grafts and a plaster cast were applied. The father's blood was not compatible with the patient's. Roentgenograms made seven weeks after operation showed union between

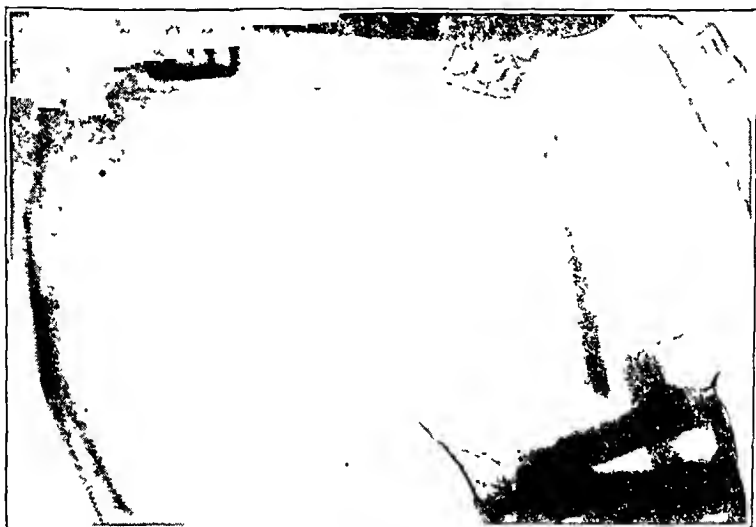


Fig. 3.—Graft from the mother's tibia applied to the left femur after resection of an area of pseudarthrosis. The condition of the right femur is shown eighteen months after application of the graft.

the bone grafts and the distal fragment of the tibia but not with the proximal fragment. On July 21 the child fell from a chair and fractured her left femur. Traction was applied, but the position of the fragments was unsatisfactory. On August 8, three months after operation, the grafts were completely united to the left tibia. On August 18 an open reduction of the left femur was done, and three pieces of bone, which had been removed from the father's tibia on May 15 and subsequently refrigerated in a sterile tube, were tied with chromic catgut to the femur. A plaster spica was applied to the left lower extremity. On November 3, six months after the operation on the tibia and two and one-half months after application of grafts to the femur, the spica was removed, and a posterior splint was applied. Union was present in the femur and the tibia, although slight bending of the tibia was possible. Roentgenograms showed union of the grafts to both the femur and the tibia. Following this, a transverse fracture occurred in

the left tibia below the grafts. This united. The child was discharged from the hospital on June 22, 1931, thirteen months after the operation on the tibia. Weight bearing was not yet permitted but was begun in October 1931. Braces were advised, but the parents refused to have them. On June 19, 1932, she fell, fracturing the middle third of the shaft of the left femur and the middle third of the right tibia and fibula. There was no displacement of the latter. The femur was treated by traction. During the next two years the left femur and tibia, to which the grafts had been applied, became larger and stronger. A marked



Fig. 4.—The result nine years after operation on the right femur and seven and one-half years after that on the left femur.

anterior bowing of the right tibia and fibula developed and on Oct. 6, 1933, this was corrected by osteotomy without the use of bone grafts. A section of bone $1\frac{1}{2}$ inches (38 cm.) long was removed because the left lower extremity was $2\frac{3}{4}$ inches (7 cm.) short. Union occurred but was slow in taking place. The patient began to walk again five months after the operation. Braces were then applied. In spite of the fact that the bones of the legs continued to develop and become larger, she sustained a fracture of the tibia and fibula on each side as the result of a fall on April 23, 1935. The fractures united without difficulty.

CASE 3.—A. V., a 5 month old boy, was admitted to the outpatient department of the New York Orthopaedic Hospital with a fracture of the right femur. Following this he was not seen until 1926, when he returned with marked deformities of the lower extremities from numerous fractures. He never had been able to walk. There was marked angulation anteriorly and laterally in the upper third of each femur and anterior bowing of the left tibia. He presented the typical appearance of osteogenesis imperfecta, with a large cranium, blue scleras and a barrel chest. In July 1927 osteotomy of the left tibia was done for increasing deformity. In November 1927 braces were made, and with these and additional support the patient was able to stand and take a few steps. He continued to have numerous fractures of his lower extremities and of the bones of the right forearm. The anterior bowing of the left tibia recurred and progressed. The patient was admitted to the New York Orthopaedic Hospital in October 1931, at the age of 13, for correction of the deformity of the left tibia and application of a heterogeneous bone graft from a donor procured by the parents. The donor was not related to the patient, and his blood was not compatible with the patient's. On October 5 a section of bone $\frac{1}{2}$ inch (1.3 cm.) thick was removed from the left tibia at the junction of the lower and the middle third, including the site of previous fracture. The marked bowing in the upper two-thirds was corrected by another osteotomy with removal of a wedge. The ends of the fragments were notched together. A graft 6 inches (15 cm.) long by 1 inch (2.5 cm.) wide from the tibia of the donor was sutured with chromic catgut to the medial surface of the upper and lower fragments of the tibia, bridging the intermediate fragment. Several smaller grafts were placed on the outer side of the tibia and secured by chromic catgut placed around the tibia and the grafts. The periosteum could not be closed, but the bone was covered with subcutaneous fat and skin. A plaster spica was applied. The sutures were removed at the end of twelve days, at which time the wound had healed by primary union. A long leg plaster cast was substituted for the spica at the end of twelve weeks. At this time union appeared firm both by physical and by roentgenographic examination. Only a trace of callus was apparent between the tibia and the graft, however. The plaster cast was removed five weeks after operation. The alinement of the left lower extremity was now fair, with slight valgus of the lower end of the tibia. Union of the tibia was present, but the grafts appeared smaller, as though undergoing absorption. Six and one-half months after operation the patient was allowed up in braces. Eleven months after operation the smaller grafts had become incorporated with the tibia and the larger one was united at each end. The patient was last seen in September 1935, at which time union was firm in the left tibia and there was a moderate degree of anterior bowing. He was able to walk short distances by using two crutches; he was greatly impeded by his immense obesity. He had just sustained a fracture of the right humerus but had had no further fractures of his tibias.

CASE 4.—R. D., a 3 year old girl, was first seen in the clinic of the New York Orthopaedic Dispensary and Hospital on Sept. 1, 1927. The left femur had been fractured at birth, and subsequently she had had four fractures of each femur. She was the typical picture of osteogenesis imperfecta, with a large cranium, blue scleras, a barrel chest and marked deformity of the femurs. She had not walked. In July 1928 leg braces were applied, with which she afterward learned to walk. The left tibia was fractured in May 1933. She was admitted to the hospital on September 5 for correction of marked anterior bowing of the tibias. On September 8 a wedge was removed from the lower fourth of the left tibia, and two onlay grafts $\frac{3}{16}$ inch (0.5 cm.) wide, which were removed from the mother's tibia, were

tied to the patient's tibia. A plaster cast was applied. On September 25 the right tibia was operated on. Because of the marked anterior bowing, two wedge-shaped osteotomies were performed, one at the lower fifth and the other at the junction of the upper and the middle third of the tibia. An onlay graft 6 inches (15 cm.) long and $\frac{1}{4}$ inch (0.6 cm.) wide was applied. This had been removed from the mother's tibia at the time of the first operation, seventeen days before. It was preserved in a sterile test tube in a refrigerator and was autoclaved before being used. Plaster casts were removed on February 14. Union had occurred in each tibia, and the grafts had united, but the bones were very small and fragile. One week later a fracture occurred in the lower end of the left tibia at the lower end of the graft. This united without delay. Roentgenograms made in June 1934 showed increased calcification of the tibias and decreased calcification of the femur. The patient was allowed to stand in long leg braces in July 1934, but in August a plaster cast was again applied because of a fracture of the right femur, which took place in bed. Five fractures of the left humerus occurred between August 1934 and July 1935. Although the deformities of the tibias partially recurred, these bones were not fractured after the bone grafts were applied. On Sept. 19, 1935, because of six recurrent fractures in the middle of the shaft of the left humerus, an onlay graft from the mother's left tibia was applied to the humerus without attempting to correct the slight angulation present. The calcium, phosphorus and phosphatase values of the blood were normal in this patient. The mother's blood was compatible with that of the patient.

TRAUMATIC RUPTURE OF A CONGENITAL CYST OF THE CHOLEDOCHUS

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In the presentation of a case of traumatic rupture of a congenital cyst of the choledochus, we believe that we are reporting a case unique in medical history. We have found, after a rather careful search of the literature, reports of only 130 accepted true cases of congenital cyst of the choledochus, and in none of these was there a history of traumatic rupture. Wright,¹ in reporting a case of cyst of the choledochus diagnosed by roentgenographic examination, made only casual mention of another of his cases in which the patient died from rupture of a congenitally dilated common duct after a fall from a bicycle, but this case has not been recorded elsewhere in the literature. Over a period of twenty years, Judd and Greene,² of the Mayo Clinic, found only one cyst of the choledochus in a series of 17,381 consecutive operations on the bile duct. Lavenson³ stated that the first congenital cyst of the common bile duct was found by Vater in 1723.

The etiology of the condition is obscure, but it is generally considered to be of embryopathologic origin. These cystic dilatations vary in size from one 3 cm. in diameter to a cyst large enough almost to fill the abdominal cavity. The duodenal intramural portion of the duct is, as a rule, of normal size; likewise, the gallbladder and the hepatic ducts are usually normal.

The congenital aneurysmal dilatation of the common duct differs markedly from the ordinary type of dilatation found as a result of stones, stricture of the common duct or tumor of the head of the pancreas. In the usual types produced by internal or external pressure,

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1. Wright, A. Dickson: X-Ray Appearances Produced by Congenital Cystic Dilatation of the Common Bile Duct, *Brit. J. Radiol.* **8**:227-230, 1935.

2. Judd, E. Starr, and Greene, E. I.: Choledochus Cyst, *Surg., Gynec. & Obst.* **46**:317-324, 1928.

3. Lavenson, R. S.: Cysts of the Common Bile Duct, *Am. J. M. Sc.* **37**:563-570, 1909.

the biliary passages and the gallbladder enlarge as a whole, in accordance with Courvoisier's law; in the congenital type, on the other hand, the enlargement simulates local aneurysmal saccular dilatation.

Zinninger and Cash ⁴ in 1932 made an excellent review of the literature and found 82 cases which they accepted as true cases. They added a report of their own case. Gross ⁵ in 1933 reviewed 50 cases of idiopathic cyst of the choledochus in childhood and added reports of 2 cases of his own. He also reviewed 14 other cases not mentioned by Zinninger and Cash. In a review of the foreign literature ⁶ we have been able to find reports of 33 cases since 1933 that have not been mentioned by the American authors. In 1934 Weber ⁷ reported a case which was particularly interesting to us because of the presence of a slitlike tear in the wall of the cyst; however, no history of injury was obtained, and the patient died in a state of cardiac decompensation. At autopsy, the rupture was found to be due to colliquative degeneration of the hyaline fibrous tissue in the wall of the cyst. Swarthey and Weeder ⁸ in 1935 added the report of another case, that of a cyst of the choledochus with double common bile duct.

In the reported cases, palpable tumors of varying sizes, intermittent attacks of jaundice and pain have been prominent and common findings. Of the 130 cases on which the literature was available, the condition occurred most frequently in females in the ratio of 99 females to 27 males. (In 4 cases the sex was not given.) In 44 of the cases the age ranged from birth to 10 years; in 31, from 11 to 20 years; in 32, from 21 to 30 years, and in 11, from 31 to 40 years; in 10 cases the age was over 40. (The age was not given in 2 cases.) Of the 119 reported cases in which surgical treatment was employed there

4. Zinninger, M. M., and Cash, J. R.: Congenital Cystic Dilatation of the Common Bile Duct, *Arch. Surg.* **24**:77-105 (Jan.) 1932.

5. Gross, Robert E.: Idiopathic Dilatation of the Common Bile Duct in Children, *J. Pediat.* **3**:730-755, 1932.

6. (a) Backer-Grøndahl, N.: Om idiopatisk choledochuscyste, *Med. rev.*, Bergen **50**:337-354, 1933. (b) Djørup, Frans: On Idiopathic Dilatation of the Choledochus, *Acta chir. Scandinav.* **74**:479-480, 1934. (c) Murata, M.: Ueber einen dauernd geheilten Fall von idopathischer Choledochuserweiterung, *Zentralbl. f. Chir.* **62**:1269, 1935. (d) Sénèque, M. J.: Dilatation congénitale du canal cholédoque, par M. A. Tailhefer, *Bull. et mém. Soc. nat. de chir.* **60**:8-11, 1934. (e) Tavernier, M.: Dilatation congénitale du cholédoque, *Lyon chir.* **31**:595-597, 1934. (f) Ugelli, L.: Sulle dilatazioni congenite del coledoca, *Policlinico (sez. chir.)* **40**:343-355, 1933.

7. Weber, F. Parkes: Cystic Dilatation of the Common Bile-Duct, *Brit. J. Child. Dis.* **31**:27-36, 1934; Further Remarks on Cystic Dilatation of Common Bile-Duct, *ibid.* **31**:113-115, 1934.

8. Swarthey, William B., and Weeder, S. Dana: Choledochus Cyst with a Double Common Bile Duct, *Ann. Surg.* **101**:912-920, 1935.

was a mortality of 56 per cent. The condition in the remaining 10 cases was found at necropsy. In 1 case, diagnosed roentgenographically, treatment was not given.

REPORT OF A CASE

History.—R. P., aged 14 years, was admitted to the accident ward of the John Sealy Hospital at 10 a. m. on Dec. 3, 1935, complaining of severe pain in the upper part of the abdomen. About fifteen minutes prior to admission he had fallen out of a swing in the public park, striking the upper part of his abdomen across the back of a park bench. There were immediate abdominal pain and vomiting. His past medical history and the family history were unimportant.

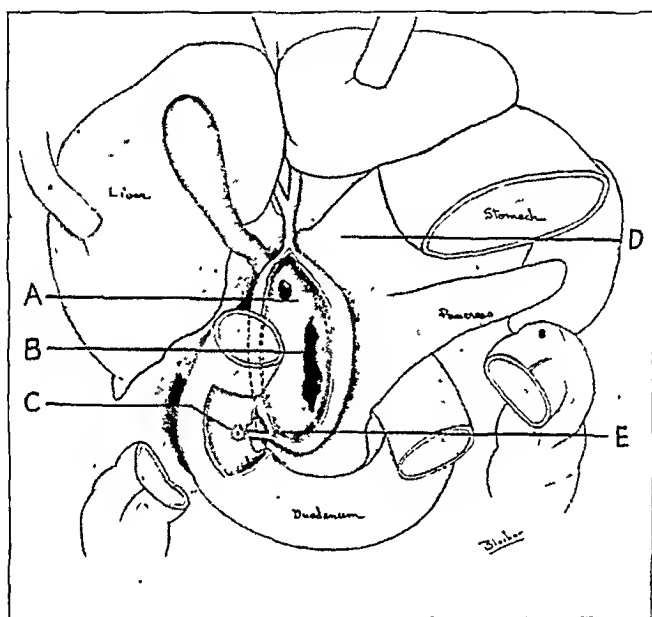


Fig. 1.—Schematic drawing of a traumatic rupture of a cyst of the congenital choledochus. The congenital cyst is indicated by *A*, the laceration in the wall of the cyst by *B*, the ampulla of Vater by *C*, extravasated bile and blood in the retro-peritoneal cellular spaces by *D* and the junction of the canal of Wirsung with the common bile duct by *E*.

Examination.—Physical examination revealed a pale Mexican boy, with anxious facies. He was very restless and tossed about on the examining table. Profuse sweating and cold, clammy skin were prominent features. A few minutes later he became quiet and lay rather listless with half closed eyes. The temperature was 97.6 F., the blood pressure 130 systolic and 90 diastolic, the pulse rate 96 and the respiratory rate 30. There was considerable pain on pressure over the whole abdomen, but it was more pronounced in the epigastrium. Muscular rigidity was marked. Dulness over the liver was still present. Rectal examination gave negative results. A specimen of urine was clear.

A tentative diagnosis of ruptured viscus was made, and the patient was taken to the operating room for immediate laparotomy.

Operation.—A right rectus incision, about $2\frac{1}{2}$ inches (6.3 cm.) in length, with its center at the level of the umbilicus, was made. The right rectus muscle was split in the line of its fibers. When the peritoneal cavity was opened, dark, straw-colored, odorless fluid was encountered. Since this fluid was recognized as a bile-stained transudate, the incision was extended upward to expose the biliary system. The gallbladder was found to be normal, and exploration of the liver revealed nothing unusual. The gallbladder and the liver were retracted upward, exposing the duodenum and a paraduodenal retroperitoneal hemorrhagic area. This area extended around the first and second portions of the duodenum, upward to the peritoneal reflection from the liver and laterally to the hepatic flexure of the colon. Incision through this layer of peritoneum showed the retroperitoneal cellular spaces to be engorged with this same type of bile-stained fluid.

At this point the patient's condition seemed to change for the worse. His pulse became more rapid, and the respirations were labored. We felt that there possibly had been a retroperitoneal rupture of the liver or bile duct, but also that the patient's condition did not warrant further exploration at this time. A stab wound was made in the right flank under the edge of the liver, and a soft rubber tube with two cigaret drains were placed in the area of retroperitoneal extravasation. The abdomen was then closed.

Immediately after the operation the patient was given 1,000 cc. of physiologic solution of sodium chloride by hypodermoclysis and 50 cc. of a 50 per cent solution of dextrose intravenously. Continuous decompression of the upper intestinal tract with a modification of the Wangensteen apparatus was also started. In spite of the foregoing measures and other routine treatment for shock, the patient died at 5:30 a.m. the next day. Permission for necropsy was obtained.

Macroscopic Examination.—Postmortem examination revealed no external lesions except the operative incisions in the wall of the abdomen. The boy was normally developed and in an excellent state of nutrition. Nearly 300 cc. of thin reddish brown fluid was found in the peritoneal cavity. The left lobe of the liver extended up, forming a peculiar hornlike projection. On the anterior and superior surfaces of the liver, a thin layer of yellow material grossly resembling bile was found. This material was also found on the inferior surface of the liver and on portions of the duodenum and pancreas.

The gallbladder was in its normal position, the tip of the fundus reaching the anterior margin of the liver. It was not enlarged. In the retroperitoneal tissues in the region of the superior border of the duodenum there was a large, greenish, fluctuant mass from which yellow fluid resembling bile could be expressed. This mass appeared to be a quantity of extravasated fluid (bile) which had dissected up the peritoneum and was seeping through into the peritoneal cavity. When the gallbladder was opened the wall was found not to be thickened, measuring from 2 to 3 mm. in thickness, and the mucosa presented no gross abnormalities.

The cystic duct could be probed with large scissors, indicating unusual dilatation. The circumference of the cystic duct was nearly 2 cm., and the thickness of the wall at this point was slightly less than that of the gallbladder. There were folds or false pockets in the mucosa of the cystic duct, which were interpreted as remnants of the spiral valve of Heister.

The hepatic ducts and the common hepatic duct did not appear to be dilated. The common bile duct was found to be a cystic mass containing dark, greenish bile. On the inferior surface, somewhat to the left side, a rupture measuring about 4 cm. in length was found. The base of the rupture was dark and ragged.

The tissue at the base of the rupture was closely associated with the greenish mass described about the superior border of the duodenum. The bile had apparently dissected up between the duct and the first portion of the duodenum. Bile also dissected through the soft tissue to the surface of the pancreas and along the peritoneal surface of the lesser peritoneal sac, but search revealed no rupture into the lesser pouch. The common duct measured 7 cm. in length, and the circumference averaged from 5 to 7 cm. The greatest circumference could be found as the ampulla was approached. The wall of the common duct was from 1 to 2 mm. in thickness. The mucosa seemed definitely thinner than that found in the gallbladder.

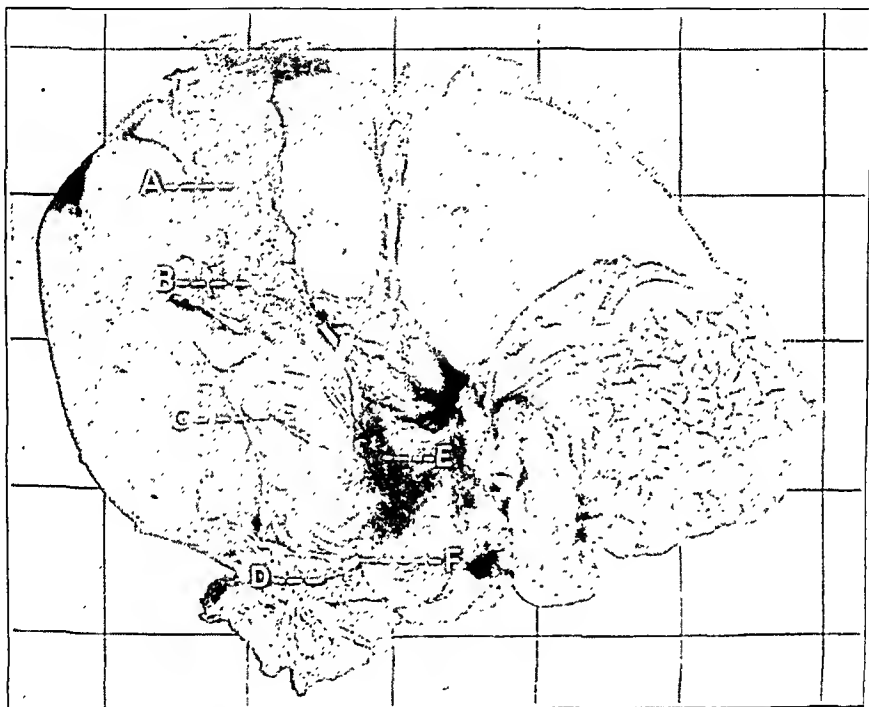


Fig. 2.—Photograph of a fixed specimen. *A* indicates the gallbladder; *B*, the cystic duct; *C*, a congenital cyst of the choledochus; *D*, the ampulla of Vater; *E*, the point of rupture of the cyst, and *F*, the junction of the pancreatic and the common bile duct.

The common duct joined the pancreatic duct through a narrow orifice at a point 2 cm. from the common orifice in the duodenum. Rather striking was the fact that the ampulla of Vater, or the common passage of the pancreatic and common bile duct, was at right angles to the common bile duct and seemingly a continuation of the duct of Wirsung. In this case, one might easily consider that the common bile duct opened into the pancreatic duct. The duct of Santorini was normal.

The liver was normal. Further examination revealed no rupture of the viscera. The heart and lungs were normal. No other anomalies were found in the body.

Microscopic Examination.—There was a little fat necrosis in the omental tissue and rather marked peritoneal inflammation in the areas nearest the rupture. In the lungs there was found some bronchopneumonia and congestion.

There was considerable bile around the pancreas, to which attention was called in the gross description. Areas of acute inflammation were found in the pancreatic tissue.



Fig. 3.—Photomicrograph of the wall of the cyst, showing the absence of muscle fibers and the increase of fibrous tissue.

The liver was normal in all respects. The gallbladder showed the usual post-mortem changes in the epithelium and mucosa but was otherwise normal. The

common duct was lined with cuboidal epithelium, which was definitely flattened as compared with normal. There was a rather mild chronic inflammatory reaction throughout the duct, and the lymphatic vessels were engorged with lymphocytes. The wall of the duct was composed of the lining epithelium (which in some areas was deficient), a relatively thick wall of fibrous tissue and the serosa. No muscle fibers could be identified in the walls of the duct.

COMMENT

The literature gives little information concerning the relation of the pancreatic duct or ducts to a cyst of the choledochus. Sènèque and Tailhefer^{6a} list cases in which the enlargement of the cyst of the choledochus occurred so near the ampulla that the pancreatic duct opened directly into the cyst.

In the case which we have presented, the pancreatic duct and the common bile duct had a common lumen for a distance of 3 cm. before entering the duodenum. That the cyst exerted no influence on the ampulla seemed certain. There were no obstructions, strictures, tumors or inflammatory processes in the biliary passage. We feel that this case goes far toward substantiating the assumption that these cysts are congenital. A large dilated cyst had developed, and yet the patient failed to suffer any discomfort at this early period. Undoubtedly, if the cyst had continued to enlarge, the patient would have experienced the pain and the gastro-intestinal symptoms described in the reported cases

SUMMARY

We have presented, we believe, the only case of a cyst of the choledochus with traumatic rupture. The fact that our patient had no previous history of illness with reference to the biliary system substantiates the patency of his choledochus. We believe that this fact also marks the etiology as congenital, particularly in this case. The rarity of finding a cyst of the choledochus is exceeded only by finding one that has ruptured.

PREVENTION OF THE FORMATION OF URINARY CALCULI IN PATIENTS WITH ORTHOPEDIC PROBLEMS

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AND

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CLEVELAND

Reports in the literature of the association of urinary calculi and diseases of the bone have been confined chiefly to the presentation of cases, and in some instances analyses of the chemical composition of the calculi have been given. Occasionally the presence of infection in the urinary tract has been noted when calculi developed during a long period of immobilization. The formation of urinary calculi under such circumstances is not a rare and unusual complication, and a few cases have been reported and discussed from the etiologic standpoint, but little thought has been given to the nature of the disease and its prevention.

The physiochemical reactions which aid or prevent the formation of urinary calculi have ceased to be matters for conjecture, and it is now recognized that a deficiency in vitamin A, infection in the urinary tract, urinary stasis, hyperparathyroidism, phosphaturia, oxaluria and excessive quantities of uric acid definitely predispose to their formation. In view of the fact that many of these predisposing factors frequently occur in patients whose convalescence requires a long period of immobilization, the formation of calculi can be minimized by the use of dietary measures in addition to the other therapeutic measures usually employed.

The following case is one in which urinary calculi developed during a long convalescence, so that when the presence of stones was first recognized the kidney was destroyed to the extent that nephrectomy was required.

REPORT OF A CASE

History.—A man 24 years of age entered the Cleveland Clinic on Jan. 2, 1929, complaining of paralysis of the legs and a stone in the right kidney. In July 1927, eighteen months before admission to the clinic, the first lumbar vertebra was fractured in an automobile accident, and the patient immediately became paralyzed from below the level of the umbilicus. This was accompanied by loss of control of the bladder and rectum. In August 1927 bilateral thrombophlebitis of the legs developed, and soon after this laminectomy was performed. In November 1927 a roentgenogram had been taken because of acute cystitis, and a large calculus was seen in the right kidney. This had not been present in July, at the time of the injury, four months previously.

From the Cleveland Clinic.

In January 1928 the patient began to use crutches. There had been considerable improvement in the function of the lower extremities, but he had to wear braces because of paralysis of the muscles of the lower part of the legs. He had no control of the rectal sphincter but was able to start the flow of urine by pressing firmly over the bladder and tightening the abdominal muscles. Roentgenograms showed that the calculus was progressively increasing in size.

Aside from the usual diseases of childhood and pneumonia at the age of 16, the patient had always had excellent health.

Physical Examination.—When the patient was seen at the clinic eighteen months after his injury, physical examination showed him to be well developed and nourished and unable to walk without the use of braces and a cane. The scar over the lower dorsal and upper lumbar vertebrae was well healed. Considerable paralysis was noted below the site of the lesion, and a complete toe drop was present. There was a marked loss of tone of the rectal sphincter.

Urologic Examination.—A stereoscopic roentgenogram showed a large stone in the right kidney, which was moderately enlarged.

Cystoscopic Examination.—The cystoscope was introduced into the bladder with ease through a relaxed internal sphincter. The bladder, which had a capacity of 300 cc., contained 2 ounces (60 cc.) of cloudy residual urine. No stones, ulcer, tumor or diverticulum was present. There was a generalized diffuse chronic inflammation of the wall of the bladder. The bladder showed trabeculation, which may previously have been rather fine, but at the time of this examination was fairly thick. The examiner received the impression that this was a neurogenic bladder, the condition of which had been improving. Five cubic centimeters of indigo carmine was injected intravenously and was seen to appear from the right ureteral orifice in seven and one-half minutes with two plus strength and from the left orifice in four minutes with four plus strength. Catheters were passed to the pelvis of each kidney, and specimens of urine were secured for study.

After the injection of 18 cc. of sodium iodide, a pyelogram showed extensive hydronephrosis of the right kidney and a large stone in the pelvis, which filled the lower calices.

Laboratory Findings.—Examination of the blood showed 4,980,000 red cells, 5,950 white cells and 90 per cent hemoglobin. The sugar content was 82 mg., the urea content 24 mg. and the creatinine content 1.5 mg. per hundred cubic centimeters of blood. The Wassermann test gave a negative reaction.

Examination of the urine showed it to be alkaline in reaction, with a specific gravity of 1.016. It contained a trace of albumin but no sugar. There were numerous white blood cells but few red cells. No casts were present, but there were numerous phosphatic crystals.

The urine from the right kidney, which contained the stone, was alkaline in reaction. It contained many red blood cells and numerous phosphatic crystals but no white cells. Examination of the sediment was negative for organisms, and repeated cultures of the specimen gave negative results. The urine from the left kidney was slightly alkaline in reaction; it contained numerous red cells and a few phosphatic crystals but no white cells. The urine from the bladder was alkaline in reaction and contained many red cells and clumps of white cells. A culture of the specimen showed *Bacillus coli* and *Staphylococcus albus*.

Since the stone was not causing the patient a great deal of discomfort, permission for operative intervention was refused, but the symptoms increased, and on

Dec. 12, 1931, four years and eight months after the injury, nephrectomy was performed on the right side. Chemical analysis of the stone after its removal showed it to be composed chiefly of calcium phosphate

At this time, we had completed our first experimental work on the use of a high vitamin A diet in the prevention of urinary calculi. Therefore, after operation, a modified high vitamin A acid ash diet was prescribed, and there has been no evidence of the further formation of calculi. The reaction of the urine has remained acid.

When the patient was admitted to the hospital after his injury, the urine was acid in reaction and no infection was present. One week later the reaction was alkaline, and it remained so throughout the entire period of immobilization. When the patient was first seen at the clinic, the urine was alkaline in reaction and was loaded with phosphates and phosphatic crystals.



Pyelogram showing extensive hydronephrosis of the right kidney and a large stone in the pelvis

HISTORICAL SURVEY

In 1855 Virchow¹ first noted the relationship between destructive lesions of the bones and pathologic calcification. Although urinary calculi were not present in any of the cases cited, he believed that the metastatic deposit of calcium consisted of the same salts which, through resorption, had disappeared from the osseous lesions and that an excess of calcium salts in the blood or hypercalcemia was an important factor in the causation of such deposits.

1. Virchow, R · Kalkmetastasen, Virchows Arch. f. path. Anat. 8:103, 1855.

The earliest reference to the association of the formation of renal calculi and conditions of the bone was noted by Bastion² in 1861. He reported the formation of calculi after a vertebral injury. In 1895 Müller³ reported eight cases in which bilateral renal calculi developed after severe spinal injury. Cabot⁴ in 1910 reported the formation of renal calculi after severe injury to the hip. In this instance a phosphatic stone was passed spontaneously, and later a stone was removed from the left ureter.

Paul,⁵ working in the Department of Soldiers' Civil Reestablishment in Toronto, Canada, observed the frequent etiologic relationship between suppuration of the bone and the formation of urinary calculi. He presented twenty cases in which suppuration of the bone had occurred and found that the urine of approximately 90 per cent of the patients was infected. The average time which elapsed between the injury and the appearance of the first renal symptom was seventeen and seven-tenths months; the longest time was forty-five months, and the shortest, four months.

Mayet⁶ in 1920 reported two instances in which renal calculi developed in a patient who was immobilized for a period of several years for Pott's disease and tuberculosis of the hip, respectively. In one of these cases the calculi were bilateral.

Taterka⁷ in 1926 reported that bilateral renal calculi developed in a patient who had a gunshot wound in the cervical portion of the spine and in another with a vertebral injury due to a fall. Vesical calculi developed in one of these patients within six months after the injury.

In 1928 O'Connor⁸ reported the formation of bilateral renal calculi and vesical calculi within five months after a crushing injury to the spine.

Reports of the association of urinary calculi and diseases of the bone have been presented more frequently since 1930. Although the "age of speed" may be conducive to a larger number of severe injuries, the apparent increase in incidence is probably due to the fact that physicians are more alert to recognize this complication.

2. Bastion, cited by Abeshouse, B. S., in discussion on Holmes and Coplan,²⁴ p. 232.

3. Müller, K.: Ueber Nephrolithiasis nach Rückenmarksverletzungen, Verhandl. d. deutsch. Gesellsch. f. Chir. **2**:253-266, 1895.

4. Cabot, H.: Remarks on the Technic of Operations for Stone in the Ureter, Boston M. & S. J. **168**:789-791, 1910.

5. Paul, H. Ernest: Bone Suppuration, the Basic Cause of Renal Calculus Following War-Wounds, J. Urol. **9**:345-365 (April) 1923.

6. Mayet, H. H., cited by Brown and Earlam.¹²

7. Taterka, Hans: Ueber Steinbildung in den Nieren nach Wirbelsäulenverletzungen, Ztschr. f. d. ges. Neurol. u. Psychiat. **105**:661-666, 1926.

8. O'Connor, V. J.: Urological Complications Following Fracture of Spine: Case Report, J. Urol. **19**:721-728 (June) 1928.

In 1930 Borman⁹ cited the case of a boy 9 years of age in whom renal and ureteral calculi developed after suppuration of the bone, and in the same year Schwarz¹⁰ reported bilateral calculi accompanying suppurative lesions of the bone. Weber¹¹ in 1931 found renal calculi associated with suppuration of the bone in nine instances.

In the more recent literature, Brown and Earlam¹² cited the relation of prolonged immobilization and infection of the urinary tract. Long periods of immobilization were required in each of the six cases they report, although injury to the bone was not the primary cause in every instance. They stated that these diseases may be associated under any of the following three conditions: (1) when immobilization is required during the treatment of a noninfective lesion, as illustrated by the case reported by Cabot in 1910; (2) when calculous formation is accompanied by septic disease of a bone, as illustrated by the cases reported by Paul in 1923; (3) when calculous formation is accompanied by injury or disease of the spine, as illustrated by the cases reported by Müller in 1895.

Goldstein and Abeshouse¹³ recently reviewed the literature on the association of urinary calculi and diseases of the bone and added fourteen cases. They pointed out the relationship between urinary lithiasis and various chronic diseases of the bone, such as osteomalacia and rickets, placing emphasis on the proper dietary management of patients with chronic diseases of the bone or injury to the bone.

Thus the literature on this subject is not extensive, and to a large extent it is confined to discussions of the association of the formation of calculi accompanying diseases of the bone, with brief consideration of the prevention of such complications. It is perhaps true that the presence of the calculi is often overlooked, as is illustrated by the few cases reported. Unless the possible presence of stones is considered, they may not be discovered, because it is well known that they may be present for years without producing pain or symptoms.

9. Borman, M. C.: Bone Suppuration and Renal Calculi in Children, *Am. J. Dis. Child.* **40**:804-812 (Oct.) 1930.

10. Schwarz, O. A.: Fall von Bechterewscher Erkrankung mit doppelseitigen Nierensteinen, *Ztschr. f. Urol.* **24**:293-294, 1930.

11. Weber, W.: Steinbildung und Knochenerkrankungen, *Ztschr. f. Urol.* **25**: 36-41, 1931.

12. Brown, R. K. L., and Earlam, M. S. S.: Relation of Prolonged Immobilization and Urinary Tract Infection to Renal Calculus Formation, *Australian & New Zealand J. Surg.* **3**:157-171 (Oct.) 1933.

13. Goldstein, A. E., and Abeshouse, B. S.: Urinary Calculi in Bone Diseases: Review of the Literature and Report of Cases, *Arch. Surg.* **31**:943-981 (Dec.) 1935.

ETIOLOGIC FACTORS

The etiologic factors which are associated with the formation of urinary calculi may be classified in the following manner: (1) infection, both local and focal; (2) stasis; (3) hyperparathyroidism; (4) nutritional deficiency, and (5) phosphaturia.

When prolonged immobilization is required, as is usual in the cases of patients with orthopedic problems, several of these factors may be aggravated, such as stasis due to injury of the spinal cord, injury to the kidney, hypercalcemia and nutritional deficiency.

Infection and Stasis.—Many observers believe that infection is the major factor in the production of urinary calculi; however, this factor may be entirely absent in the presence of a renal calculus, as is illustrated by the case reported here. Likewise, it appears logical that in other instances the formation of stones may precede infection, which occurs later, either as a result of traumatization of the kidney by calculi or after stasis occurs owing to interference with the outflow of urine from the kidney. Certainly the factors which commonly are associated with the formation of calculi influence their formation in patients with orthopedic problems.

Bugbee¹⁴ reviewed the results of operations for nephrolithiasis to determine the presence of preexisting pyelonephritis as a possible factor in the formation of renal calculi. A definite history of pyelonephritis was elicited in twenty-three cases. Treatment had been administered to seventeen patients during the initial attack, and in six the infection had been treated by other physicians. Although roentgenograms did not show the presence of a calculus when the patient was first seen, stones subsequently developed in all these patients. It is interesting to note that the urine was acid in reaction and that the colon bacillus was the offending organism during the first attack in sixteen cases; in nine of these the urine later became alkaline in reaction, and many staphylococci were present. In five cases the urine remained alkaline throughout the period of observation; in one it was neutral, and in another, both acid and alkaline reactions were noted during the period of observation. Calculi which formed in an acid urine were composed of calcium oxalate, and those which formed in alkaline urine were largely phosphatic in composition.

Keyser,¹⁵ at the Mayo Clinic, reported obtaining positive cultures of the urine from the bladder of six of his twelve patients and a negative culture of the urine from one; culture of the urine of the five

14. Bugbee, H. O.: Recurring Pyelonephritis as Etiological Factor in Nephrolithiasis, *Tr. Am. A. Genito-Urin. Surgeons* **25**:121-131, 1932.

15. Keyser, L. D.: Relationship of Urinary Infections to Recurrent Calculi, *J. Urol.* **31**:219-238 (Feb.) 1934.

other patients was not reported. Paul⁵ reported twenty cases in which renal calculi developed after suppuration of the bone due to war injuries. Subsequently, urinary infection was noted in 90 per cent of the cases, and Paul expressed the belief that urinary infection was the primary cause of calculous formation.

Barr and Charles¹⁶ expressed the belief that infection, in common with stasis and an increase of calcium excretion in the urine, plays considerable part in the formation of stones. Northfield,¹⁷ Weber,¹¹ Wallenstein¹⁸ and others have cited the relationship of infection of the urinary tract and subsequent calculous formation after suppuration of the bone. In many of these cases there was injury to the spinal cord, with subsequent paralysis of the bladder and, after routine catheterization, cystitis developed, which later was followed by ascending renal infection.

Some authors have even recommended cystotomy in an effort to prevent such complications. Although calculi have been reported to develop in aseptic kidneys or in the presence of colon bacilli, this is not as frequent a finding as when urea-splitting organisms are present. Such organisms definitely contribute to calculous formation owing to the precipitation of the alkaline inorganic salts, such as phosphates and carbonates of calcium and magnesium. With this type of infection, calculi may develop with considerable rapidity, enlarge rapidly and eventually destroy the kidney.

Hyperparathyroidism.—Numerous studies have been made to demonstrate the relation between hyperparathyroidism and the formation of calculi, and the most important of these are the reports of Albright and Bloomberg,¹⁹ Barney²⁰ and Chute.²¹ Albright and Bloomberg reported twenty-three proved cases of hyperparathyroidism among which roentgen studies revealed the presence of renal calculi in fifteen. Laboratory examination showed a high level of serum calcium, a low level

16. Barr, D. P., and Charles, Cecil M.: Relation of Diseases of Bone to Arterial Calcification and Urolithiasis, in Contributions to the Medical Sciences in Honor of Dr. Emanuel Libman by His Pupils, Friends and Colleagues, New York, International Press, 1932, vol. 1, pp. 155-179.

17. Northfield, D. W. C.: Case of Fractured Pelvis Followed by Unusual Complications, *Guy's Hosp. Rep.* **83**:252-256 (April) 1933.

18. Wallenstein, S.: Renal Calculi Following Fracture of Spine, *South. M. J.* **24**:675-678 (Aug.) 1931.

19. Albright, F., and Bloomberg, E.: Hyperparathyroidism and Renal Disease with Note as to Formation of Calcium Casts in This Disease, *Tr. Am. A. Genito-Urin. Surgeons* **27**:195-202, 1934.

20. Barney, D.: Recurrent Renal Calculi, *Surg., Gynec. & Obst.* **35**:743-748 (Dec.) 1922.

21. Chute, R.: Vital Importance of Relation of Hyperparathyroidism to Formation of Certain Urinary Calculi—and Its Remedy, *New England J. Med.* **210**: 1251-1253 (June 14) 1934.

of serum phosphorus and an increase in the excretion of calcium and phosphorus in the urine. Disease of the bone without a coexisting renal pathologic process was present in only five cases in this series. These findings suggest that renal disease is a more frequent complication of hyperparathyroidism than is osseous disease.

In numerous cases renal colic has been reported as the presenting symptom leading to the diagnosis of hyperparathyroidism, which soon was associated with disease of the bone. Hunter and Turnbull²² in 1931 reported the association of hyperparathyroidism and generalized osteitis fibrosa with renal calculi, and in several cases renal colic was the presenting symptom.

In our recent series of two hundred and ten cases in which complete studies of the blood have been made findings indicative of the presence of hyperparathyroidism were observed in only one instance, and this was verified by the removal of an adenoma of the parathyroid gland.

Vitamin A Deficiency.—Although a definite history of deficiency in the diet may not be elicited and although clinical evidence of such deficiency may not be well marked, one cannot be certain that a continuous mild degree of deficiency may not be present. Therefore, as a routine, we use the biophotometer test (for determination of the light threshold), which is the most accurate method available for estimating vitamin A deficiency in cases of renal calculi. In a recent clinical study of cases of nephrolithiasis, a positive reaction to the biophotometer test was obtained in thirty; questionable results were secured in four, and normal readings, in eleven. Jeans²³ recently found that 26 per cent of a rural group and 53 per cent of a village group of Iowa children presented evidence of vitamin A deficiency as judged by means of this test. In an urban group, the percentage was still higher, but in all except three of the children from the village and the rural district who remained under observation, normal dark adaptation developed after a period of ingestion of vitamin A or carotene. In one of our cases in which hyperparathyroidism was associated with bilateral renal calculi, we secured the lowest reading we have ever seen in any case of renal calculi, indicating that severe deficiency in vitamin A existed.

NUTRITIONAL DEFICIENCY

Several factors must be taken into consideration in determining the presence of nutritional deficiency. The seasonal influence of the

22. Hunter, Donald, and Turnbull, H. M.: Hyperparathyroidism, Generalized Osteitis Fibrosa with Observations upon Bones, Parathyroid Tumors, and Normal Parathyroid Glands, *Brit. J. Surg.* 19:203-284 (Oct.) 1931.

23. Jeans, P. C., and Zentmire, Z.: The Prevalence of Vitamin A Deficiency Among Iowa Children, *J. A. M. A.* 106:996-997 (March 21) 1936.

vitamin A content of dairy products and eggs has been cited in previous publications and has been well worked out by the Ohio Experimental Station. Likewise, in the so-called "stone areas" a definite deficiency in the diet has been shown to be present.

Vitamin A is essential to the diet because adequate amounts maintain the integrity of the epithelial structures, whereas when a deficiency in vitamin A exists, stratified epithelium is noted in the bladder, the ureters and the renal pelves. This may be followed by desquamation or ulceration of the mucosa of the renal pelves, and in the presence of strongly alkaline urine the phosphates and carbonates of calcium and phosphorus may adhere to the fibrin poured out from the denuded area. These small accumulations may be voided spontaneously, or they may gradually enlarge and drop into the dependent lower calix. Thus the initial calculus is formed, and further enlargement occurs as the phosphates and carbonates adhere to this nucleus. In the presence of acid urine, uric acid calculi may develop in like manner, while the oxalates are precipitated in a wide range of urinary reactions.

Phosphaturia.—Increased elimination of oxalates and uric acid in the urine as well as a persistent phosphaturia is associated with calculous formation. The urine may become alkaline temporarily, owing to the ingestion of an excess of alkaline ash food, or a temporary phosphaturia may be associated with a metabolic disorder. In either case an increase of phosphates in the total amount of body fluids is found. Likewise, disturbances in the function of the large bowel may produce a more permanent phosphaturia. Under such circumstances the usual amounts of earthy phosphates are not eliminated by the bowel, and a portion of the burden is shifted to the urinary tract. Phosphaturia in the presence of infections of a urea-splitting nature becomes an important factor in the formation of calculi. Such urine is found to be alkaline in reaction, and the phosphates and carbonates are precipitated rapidly, thus producing stones in a short time. Dietary control of the urinary reactions by changing the hydrogen ion concentration and eradication of the infection will minimize the formation of calculi.

ADDITIONAL ETIOLOGIC FACTORS

The factors just discussed are among those which commonly are seen in the presence of urolithiasis. In cases of coexisting disease of the bone of long standing, especially when injury to the vertebral column and subsequent pressure on the spinal cord take place or extensive suppurating wounds are found, additional factors may be responsible.

Injury to the Kidney.—After a primary intrinsic lesion of the kidney occurs. Rupture of a considerable area of the renal tissue or even

of small vessels causes extravasation of blood into the renal pelvis, and these blood clots serve as nuclei on which calculi may have their origin. Such intrinsic lesions may be slow to heal, and subsequent infection ascending from an inactive bladder constitutes a fertile field for the formation of calculi.

Holmes and Coplan²⁴ pointed out the importance of secondary or extrinsic injury of the urinary tract due to paralysis. Hollander²⁵ maintained that after an injury to the spinal cord there is an interruption of the reflex arc concerned in expression of the urine from the renal papillae into the pelvis, together with a loss of muscular activity of the bladder, ureter and pelvis. This derangement of the entire upper part of the urinary tract favors urinary stasis and infection. Additional changes soon occur, such as decomposition and ammoniacal formation of urinary salts with the ultimate formation of phosphatic calculi.

Wallenstein²⁶ reported a case of crushing injury to the spine followed by paralysis. He expressed the belief that suprapubic cystotomy is indicated in such instances and that it is probably the best procedure for complete or incomplete transverse lesions of the cord, as both stasis and infections are eliminated.

Prolonged Immobilization and Stasis.—Extensive and chronic osteomyelitis, infected compound fractures, fractures of the spine and tuberculosis of the spine or hip require long periods of immobilization. As has been pointed out, such conditions are usually complicated by general infection, by infection of the urinary tract and stasis and by lack of essentials in nutrition (due to loss of appetite from inactivity) to such an extent that it is difficult to determine the primary factor in the formation of calculi.

The importance of prolonged immobilization and consequent stasis has been emphasized by Brown and Earlam,¹² who reviewed the literature and cited the relation between prolonged immobilization and the formation of renal calculi in six illustrative cases. They stated that urinary infection leads to accelerated growth of calculi but that this factor alone cannot be responsible for the formation of stones. The formation of calculi in the presence of noninfected lesions has been reported by Cabot⁴ and Joly.²⁶ Brown and Earlam¹² pointed out that when a patient undergoes prolonged immobilization in the dorsal decubi-

24. Holmes, R. J., and Coplan, M. M: Extensive Bilateral Renal Calculosis of Rapid Development Following Fracture of Vertebrae. *South. M. J.* **27**:228-233 (March) 1934.

25. Hollander, cited by Abeshouse, B. S., in discussion on Holmes and Coplan,²⁴ p. 232.

26. Joly, J. Swift: *Stone and Calculous Disease of the Urinary Organs*. St Louis, C. V. Mosby Company. 1929. pp 85-87.

tus position, the minor calices occupy the most dependent position, while the pelvis is drained at its highest point. In the majority of instances no harm is done if infection is not present, the physical condition of the urine being such that crystals are not deposited. In a patient, however, in whom deposition of crystals occasionally occurs and in whom crystals normally would pass from time to time, stasis in the minor calices can easily constitute the additional factor necessary for the production of calculi.

Prolonged immobilization, by interfering with drainage from the pelvis and calices, may provide sufficient time for a change in hydrogen ion concentration of the urine to take place and for the precipitation of crystals which ordinarily would not occur. We know that precipitation of carbonates and phosphates occurs only in an alkaline urine. This is true also of the precipitation of uric acid crystals which occurs when the hydrogen ion concentration is shifted strongly to the acid side.

HYPERCALCEMIA

After vertebral injury and accompanying paralysis, the formation of calculi composed of calcium has been attributed to demineralization of the bones and muscular inactivity during immobilization.

Hyperparathyroidism is characterized by marked hypercalcemia, and the calcium output in the urine is much greater than normal. In many cases in which no disturbances of the parathyroid glands are demonstrable but in which muscular inactivity and osseous destruction and reconstruction occur, a marked increase in the calcium content of the blood is found. Schwarz,¹⁰ Barr and Charles¹⁶ and Holmes and Coplan²⁴ pointed out the significance of this fact. Normally, about 90 per cent of the calcium taken into the body is excreted through the intestinal tract and 10 per cent through the urinary tract. These percentages vary markedly, however, and it is well known that the rates may be reversed easily, the greatest burden being placed on the kidney. However, it is probably true that the destructive and constructive processes in the bone will be affected by the consequent increase of calcium in the circulating blood and a greater excretion of salts in the urine. Roentgen examination reveals the degree to which decalcification of bone may occur during complete immobilization for a long time. Usually, general infection, infection of the urinary tract and malnutrition are also present, so that no single factor can be held responsible for the abnormal deposit of calcium.

CHEMICAL COMPOSITION OF CALCULI

In reviewing the literature, it is noted that a chemical analysis of the calculi has been made in only a few cases. However, the stones that have been analyzed have been found to be composed chiefly of calcium

phosphate. In one case reported by Brown and Earlam¹² the calculus was composed chiefly of calcium phosphate, but traces of calcium oxalate were also present.

In the series of twenty cases reported by Paul⁵ calcium oxalate was the principal constituent in two instances, but the chemical constituents were not reported in the others. Brown and Earlam,¹² Taterka,⁷ Borman,⁹ Weber¹¹ and Holmes and Coplan²⁴ found calculi to be composed of calcium phosphate. In the four cases of calculi associated with fractures which I have seen in the past year, calcium phosphate was the principal constituent of the stones. Thus, it is apparent that the majority of the calculi which develop in patients with orthopedic problems are formed in the presence of an alkaline urine. Goldstein and Abeshouse¹³ reported that chemical analyses showed that the stones in one of their cases were of mixed phosphatic type.

TYPE OF INFECTION PRESENT

Cultures have not been made of the organisms which have been present in the genito-urinary tract in most of the cases reported in the literature, and little mention is made as to whether the organism had the urea-splitting property. In case 4 cited by Brown and Earlam¹² an infection due to *Proteus* was present, and in case 6 *Staph. albus* was the offending organism. In the series of cases reported by Paul⁵ the most common organisms were *Staph. aureus* and *B. coli*. In our series of six cases *Proteus* was cultured in two instances; *Staph. aureus* was present in one case, *Proteus ammoniae* in two and *Bacillus Thompsoni* in one. In four of the six cases the organism had the property of splitting urea strongly, and in one case this occurred but faintly.

SYMPTOMS AND DIAGNOSIS

When an orthopedic condition has existed for a long time, the diagnosis of complicating urinary calculi presents a greater problem than in the usual case of urolithiasis, because attention is directed largely to the major orthopedic problem with its usual complications. The patient is immobilized, and, owing to the inactivity, symptoms of renal calculi do not present themselves as early as they might in the active patient. An early diagnosis is important, since the formation of stones occurs more rapidly, and this means greater renal damage. The large number of contributing factors, such as hypercalcemia, immobilization and infection, which are associated in the majority of cases, also makes early diagnosis imperative, or, even better, the prevention of such complications should be sought.

In the cases reported in the literature, calculi were found as early as three weeks after immobilization. Holmes and Coplan²⁴ reported

that they had found stones four weeks after injury, and O'Connor⁸ stated that he found bilateral renal calculi which developed within five months after injury and that during that time they had become so extensive that removal was impossible. In most instances diagnosis was made during the time of convalescence, but in a great number diagnosis was not made until after the patient became active.

Another reason why diagnosis is delayed is the fact that accompanying urinary infection and often urinary retention due to paralysis tend to obscure early signs of calculi. Burning, pyuria and perhaps frequency of urination, which are commonly associated with calculi, are already present. With severe infections, at least microscopic if not gross, hematuria may be found. In the cases reported hematuria was the most frequent presenting symptom, and this finding prompted many of the physicians to make a roentgen study which revealed the calculi. The third reason why the diagnosis of calculi is delayed in vertebral and pelvic injuries is that one tends to associate any accompanying renal colic with the pain due to the injury rather than with pain due to the complication. Renal colic was the second most common presenting symptom which suggested roentgen study in the cases reported. In many cases, however, calculi were so large that they were more or less fixed and little colic occurred. In other cases calculi were discovered accidentally during the course of roentgen examination. When calculi were found to be present after immobilization, renal colic, hematuria and passing of small stones or gravel were the presenting symptoms.

TREATMENT

When calculi are first noted, they may be producing an obstruction and destroying the renal parenchyma so that surgical intervention is essential to prevent complete destruction of the kidney. In other instances the calculi, when first discovered, may already have destroyed the kidney, and a marked infection may be present which requires nephrectomy. Our problem, therefore, is to prevent or minimize calculous formation which occurs during the long period of immobilization.

In reviewing the cases that have been reported in the literature and those that we have seen at the clinic, we are immediately impressed with the number in which alkaline urine was present during the period of immobilization. Therefore, the calculi which formed should consist of salts precipitated in a urine with a p_H on the alkaline side. This is true, and in cases in which chemical analyses were made, calcium phosphate was the chief chemical constituent. In two cases traces of calcium oxalate were also present. In order to prevent the formation of stones, we believe that patients suffering from fractures or osteomyelitis in whom a long period of immobilization is required should be placed on a dietary regimen in addition to other therapeutic procedures during this period.

PREVENTION AND TREATMENT OF INFECTION

Whether or not drainage should be instituted by means of a catheter after injuries to the spine is still a controversial subject. Personally, we believe that, if possible, spontaneous development of overflow is preferable. When drainage is instituted with a catheter, however, extreme care must be taken to minimize infection of the bladder which may result in subsequent renal infection. Catheterization under sterile precautions, irrigations of the bladder with a solution of potassium permanganate (1:4,000) and instillations of mild silver protein will help to prevent this complication. Likewise, urinary antiseptics, preferably sodium dihydrogen phosphate and methenamine, which render the urine acid in reaction, should be administered by mouth in large doses to aid in the eradication of the infection. The use of alkaline therapy should not be employed for any length of time. Careful examination of the urine at frequent intervals is essential to ascertain the number of pus cells in the urine, the type of organism present and whether precipitation of phosphates and carbonates is occurring.

The prevention of infection of the kidneys and the minimization of infection in the bladder cannot be emphasized too greatly. If the patient is maintained in a recumbent position, the position should be changed frequently if it is at all possible. Obviously, in cases of fracture of the pelvis or spine this may not be possible, but in cases of injury or infection of the leg such a shift in position may be feasible. Finally, by use of the high vitamin A acid ash diet, the p_H of the urine is shifted to the acid side to a level of 5 or 5.2, at which point the phosphates and carbonates of calcium and magnesium are held in complete solution, and precipitation of these salts does not occur. Vitamin A is administered in the form of two capsules of halibut liver oil or carotene in oil daily. Vitamin A is prescribed (1) for its effect in maintaining the integrity of the epithelium of the genito-urinary tract, (2) for the correction of vitamin A deficiency, if present, or the prevention of its development, and (3) for increasing the resistance of the patient to infection.

Obviously, in this group of patients a specimen of urine cannot be taken from the kidneys, and we must rely on the p_H of the urine from the bladder as a guide to the excess of acid ash to be included in the diet. In the absence of a urea-splitting infection in the kidney, the p_H of the urine from the bladder will usually suffice. The basic diet consists of an excess acid ash of 17.3 cc., which is varied daily according to the p_H of the urine.

The purpose of this diet is to furnish an adequate high vitamin diet in which the total acid ash exceeds the total basic ash. To accom-

plish this, it is absolutely necessary that no salt be used for seasoning foods, either in cooking or at the table.

The following foods, in the amounts designated, must be included in the diet daily.

A. Acid Ash Foods (Minimum Amounts) :

1. Cereal—any one of the following measured servings (2 cc. excess acid ash) :

	Amount
Cornflakes	1 cup heaping
Cornmeal (cooked)	$\frac{2}{3}$ cup
Farina (cooked)	$\frac{2}{3}$ cup
Oatmeal (cooked)	$\frac{1}{2}$ cup
Puffed wheat	1 cup scant
Puffed rice	1 cup heaping
Rice (cooked)	$\frac{1}{2}$ cup scant
Shredded wheat	$\frac{1}{2}$ biscuit

2. Meat—any two of the following measured servings (12 cc. each) :

	Amount
Beef, loin, medium fat	4 by $4\frac{1}{4}$ by $\frac{1}{2}$ inch
Chicken, broiled	One-half
Chicken, stewed	Breast or thigh plus leg
Cheese, cheddar	$3\frac{1}{2}$ by 2 by 1 inch
Codfish, fresh, cooked	$\frac{1}{4}$ cup
Eggs	2
Frankfurters, large	2
Halibut	4 by 2 by 1 inch
Ham, fresh	$4\frac{1}{2}$ by 3 by $\frac{1}{4}$ inch
Heart, beef	$2\frac{1}{2}$ by 3 by 1 inch
Kidney, veal	$\frac{3}{4}$ cup
Lamb chop	3 medium size
Lamb roast	5 by 5 by $\frac{1}{4}$ inch
Liver, beef	3 by $6\frac{1}{2}$ by $\frac{1}{2}$ inch
Mackerel, fresh	2 by 4 by 1 inch
Oysters, very large	3
Pork chop, thick	1
Salmon, fresh	3 by 4 by $\frac{3}{4}$ inch
Salmon, canned	$\frac{1}{2}$ cup packed
Trout	$2\frac{1}{2}$ by 3 by 1 inch
Turkey, 2 slices	2 by 3 by $\frac{1}{4}$ inch
Veal chop	1
Veal roast	3 by $2\frac{1}{2}$ by $\frac{1}{8}$ inch
White fish	$2\frac{1}{4}$ by 3 by 1 inch

3. Bread—whole wheat—5 slices (2.2 cc. each)

4. Eggs—two (5.5 cc. each)

5 Miscellaneous—any one of the following measured servings (2 cc.):

Macaroni	$\frac{3}{4}$ cup
Spaghetti	$\frac{1}{2}$ cup
Rice	$\frac{1}{2}$ cup
Corn	$\frac{1}{2}$ cup
Plain cake	$1\frac{3}{4}$ by $1\frac{3}{4}$ by $1\frac{1}{4}$ inches

B. Alkaline Ash Foods (Maximum Amounts):

1. Milk—1 pint (7.2 cc.)
2. Cream— $\frac{1}{4}$ cup (0.3 cc.)
3. Fruits and Vegetables—list to be given later (excess of basic ash not to exceed 25 cc.)

C. Concentrated Vitamin Foods:

1. Yeast—2 cakes
2. Cod liver oil—2 tablespoons; or halibut liver oil, 2 capsules before each meal
3. Wheat germ—2 tablespoons to be added to cereal

Fruits and vegetables shall be chosen from the following lists only. Any combination of fruits and vegetables may be selected, but the total excess basic ash in the selected combination must not exceed 25 cc. daily.

Fruit	Amount	Cc. of Excess Basic Ash
Watermelon	$2\frac{1}{2}$ by $2\frac{1}{2}$ by $\frac{1}{2}$ inch	2.7
Grapes	$\frac{1}{2}$ cup or 24 grapes	2.7
Pear	1 medium	3.6
Apple	1 small	3.7
Grape juice	$\frac{1}{2}$ cup	3.9
Lemon juice	$\frac{1}{2}$ cup	4.1
Cherry juice	$\frac{1}{2}$ cup	4.4
Orange juice	$\frac{1}{2}$ cup	4.5
Raspberry juice	$\frac{1}{2}$ cup	4.9
Peach	1 medium	5.0
Lemon	1 medium	5.5
Banana	$\frac{3}{4}$ cup or $\frac{1}{2}$ large	5.6
Orange	1 medium	5.6
Cherries	$\frac{2}{3}$ cup	6.1
Apricots	2 medium	6.8
Pineapple	$\frac{2}{3}$ cup diced	6.8
Muskmelon	$\frac{1}{2}$ cup	7.5
Rhubarb	$\frac{1}{2}$ cup	8.6

Vegetable	Amount	Cc. of Excess Basic Ash
Asparagus	$\frac{1}{2}$ cup	0.8
Green peas	$\frac{3}{4}$ cup	1.3
Onions	$\frac{1}{2}$ cup	1.5
Pumpkin	$\frac{1}{2}$ cup cooked	1.5
Turnips	$\frac{1}{2}$ cup cooked	2.7

Vegetable	Amount	Cc. of Excess Basic Ash
Squash	$\frac{1}{2}$ cup mashed	2.8
Radishes	10	2.9
Mushrooms	$\frac{1}{2}$ cup canned	4.0
Cauliflower	$\frac{2}{3}$ cup cooked	5.3
String beans	$\frac{2}{3}$ cup cooked	5.4
Tomatoes	$\frac{1}{2}$ cup	5.6
Cabbage	$\frac{2}{3}$ cup cooked; $1\frac{1}{2}$ raw	6.0
Tomato juice	$\frac{1}{2}$ cup	6.2
Sweet potato	$\frac{1}{2}$ medium size	6.7
White potato	1 potato $2\frac{1}{2}$ inches diameter	7.0
Lettuce	$\frac{1}{4}$ head or 16 leaves	7.4
Celery	4 stalks or $\frac{3}{4}$ cup	7.8
Cucumber	$\frac{1}{3}$ cup sliced	7.9
Rutabagas	$\frac{1}{2}$ cup mashed	8.5
Carrots	5.8 cup	10.8
Beets	$\frac{2}{3}$ cup	10.9

Note.—A few samples of permitted fruit and vegetable combinations, with the cubic centimeters of excess basic ash, are:

Orange juice, $\frac{1}{2}$ cup	4.5	Apple, one	3.7	Muskmelon, $\frac{1}{2}$ cup	7.5
Grapes, 24	2.7	Pineapple, $\frac{2}{3}$ cup	6.8	Apple sauce, 1 apple	3.7
Cauliflower, $\frac{2}{3}$ cup	5.3	Peas, $\frac{3}{4}$ cup	1.3	Tomato, $\frac{1}{2}$ cup	5.6
Tomato, $\frac{1}{2}$ cup	5.6	Cabbage, $\frac{3}{4}$ cup raw	3.0	Asparagus, $\frac{1}{2}$ cup	0.8
Potato, 1 medium	7.0	Potato, one	7.0	Lettuce, $\frac{1}{4}$ head	7.4
Totals	25.1		21.8		25.0

In addition, the following acid and neutral foods may be used as desired:

Acid Foods

Cranberries
Flour
Plain cookies
Pastry with custard or
allowed amounts of fruit
fillings
English walnuts
Popcorn, no salt
Unsalted peanuts
Unsalted crackers

Neutral Foods

Sweet butter
Candy—no chocolate bars
Cornstarch
Lard
Olive oil
Salad oil
Mayonnaise
Sugar
Tapioca
Tea
Coffee or
Kaffee Hag
Postum

The following list contains a few striking examples of foods which must be omitted because of their extremely high basic ash content.

Almonds	Olives
Beet greens	Parsnips
Dandelion greens	Raisins
Figs	Spinach
Molasses	Dried fruits and vegetables

Suggested Plan of Menu

Breakfast:

Fruit
Cereal and wheat germ
Eggs, two
Bread, whole wheat
Salt-free butter
Milk
Cream
Sugar
Beverage

Sample Menu

Grapes
Oatmeal and 2 tablespoons wheat germ
Scrambled eggs
Toast, whole wheat, 2 slices
Butter, 2 squares
Milk, $\frac{1}{2}$ pint
Cream, $\frac{1}{4}$ cup
Sugar
Coffee

Lunch:

Meat
Rice or substitute (see miscellaneous)
Vegetable or salad
Fruit
Bread, whole wheat
Salt-free butter
Beverage

Veal chop
Steamed rice
Sliced tomatoes
Baked apple
Whole wheat bread, $1\frac{1}{2}$ slices
Butter, 2 squares
Milk, 1 glass

Dinner:

Meat
Vegetable
Vegetable or salad
Dessert
Bread, whole wheat
Salt-free butter
Cream
Sugar
Beverage

Roast beef
Potato
String beans
Tapioca cream pudding
Whole wheat bread, $1\frac{1}{2}$ slices
Butter, 2 squares
Cream
Sugar
Coffee

Note.—One pint of milk is to be used each day, in any form

In the absence of infection, an excess of 25 cc. of acid ash in the diet usually suffices to reduce the p_H of the urine to 5 or 5.2. When an infection is present, the acid ash content may be increased, and acidifying agents, such as ammonium chloride in enteric coated pills, may be used in addition to the diet. The diet is well balanced in all

respects aside from the excess of acid ash. The specimen of urine from the bladder should be secured at least three times weekly, and the sediment should be studied for crystals and for the type of precipitate which is present. Likewise, culture of the urine, determination of the p_H and stained smear of the sediment should be made. If crystals or sediments which precipitate in an acid urine are present while the patient is on the acid ash diet, the excess acid ash in the diet should be reduced to the point at which this precipitation does not occur. Thus, each patient must be individualized, and the diet varied according to the p_H of the urine and type of crystals that are precipitated.

CONCLUSIONS

The development of renal calculi in patients with orthopedic problems, in whom prolonged immobilization is necessary, is not as rare as we are led to believe from reports in the literature.

Measures to prevent infection of the genito-urinary tract should be employed constantly.

Frequent examination of the urine should be done while the patient is being treated.

Shifting the p_H of the urine to the acid side to a level of from 5 to 5.2, where precipitation of the alkaline salts does not occur, is of aid in minimizing the formation of the types of calculi reported in the literature.

The high vitamin A acid ash diet is of value in securing the desired p_H of the urine and preventing precipitation of phosphates and carbonates of calcium and magnesium, which are the chemical constituents of the calculi which develop in these patients. Likewise, by the use of this diet, we are able to maintain the patients on a well balanced diet during the period of immobilization.

A roentgenogram should be taken before the patient leaves the hospital, to rule out the possibility of a silent renal calculus.

PHLEGMON OF THE COLON

REPORT OF A CASE

JOHN BURKE, M.D.

BUFFALO

The gastro-intestinal tract is subject to every sort of inflammatory process, ranging in severity from a simple catarrhal type to a definite phlegmon. As in other organ systems, the milder types of inflammation are overwhelmingly more frequent. Among the least frequent types of lesion is the phlegmon. It was first described by Sand in 1700.

Phlegmon is found with a frequency which decreases in almost inverse proportion to the distance of its site from the stomach. Finsterer in 1928 collected from the literature and from his own records reports of two hundred and ninety-six cases of phlegmon of the stomach. There has been no definitive study of phlegmon of the small intestine in recent years comparable with Finsterer's monograph. However, it was necessary for me to review most of the reported cases while searching for those of phlegmon of the colon, and it is my impression that there are about one hundred cases of phlegmon of the small bowel reported. Goldschmidt reported the first case involving the large intestine in 1887, and since that time about fifty cases have been reported. The word "about" is used advisedly, as I am not at all certain that I have been able to find all of the reported cases. Some of the cases herein abstracted were found by chance, having been reported under titles considerably remote from "phlegmon of the colon." Of these cases I am presenting twenty-seven as representing "pure" phlegmon of the large intestine, at least to the extent that they do not appear to represent the spread of infection from an adjacent inflamed appendix or diverticulum. Fenkner has reported many examples of this lesion which I have not included because the accompanying data have been too meager for analysis. It is perhaps appropriate at this time to say that Fenkner considered this lesion as occurring frequently in milder forms, running its course undiscovered. He expressed the belief that the thin veil-like adhesions often found attached to the cecum and ascending colon are the end-result of a healed phlegmon, and he (in his article published in 1925) gave rather interesting evidence in support of his hypothesis. Most of the authors are not of his opinion, that the resulting stenosis will eventually require operation.

Abstracts of the reported cases, together with my case, follow.

CASES FROM THE LITERATURE

GOLDSCHMIDT'S CASE, 1887.—A woman aged 41 had been ill six days. Her temperature was 39.6 C. (103.3 F.). She had bronchopneumonia and abdominal distention on admission to the hospital. Vomiting and abdominal pain developed two days later. Death occurred thirteen days after the onset. Postmortem examination showed bilateral bronchopneumonia. The small and large intestine (limit not stated) were swollen and discolored, with a thickened wall showing the picture of an acute inflammatory process. No microscopic studies were mentioned.

DOWD'S CASE, 1912.—A man aged 23 was taken ill two and one-half days before admission to the hospital, with severe abdominal pain, nausea and bloody diarrhea. On admission he showed prostration and spasm of the left rectus muscle. The temperature was 98 F. At operation the colon from the sigmoid to the hepatic flexure was angry red, swollen and thick-walled. It was resected, and the patient recovered. Histologic examination showed infiltration of all the coats with leukocytes, lymphocytes and plasma cells. A purulent exudate was found on the mucosa. The reaction was most marked in the submucosa. Streptococci were found in the submucosa.

MÜLLER'S CASE, 1914.—A man aged 51 was seized with a sudden pain in the right side of the abdomen. Examination showed abdominal distention and diffuse tenderness, most marked at MacBurney's point. A diagnosis of perityphlitis was made. At operation the appendix was found to be anemic, and there was much turbid exudate in the pelvis. (The surgeon made a note of the discrepancy between the appendix and the exudate.) The patient died the following day with signs of peritonitis. At postmortem examination 400 cc. of thick red-yellow fluid was found in the abdomen. The colon and small bowel were dirty brown and edematous. The serosa was covered with a gelatinous coagulum for 20 cm. on the cecum and 25 cm. on the ileum. Microscopic examination showed that the most marked changes were in the submucosa. There were polymorphonuclear infiltration, areas of necrosis, marked interstitial edema and masses of streptococci and gram-positive bacilli in the tissues. There was a thin deposit of fibrin on the serosa, and streptococci were found in all coats.

VON SAAR'S CASE, 1915.—A youth aged 21 complained of a pain about the navel the day before admission to the hospital. Vomiting and an increase in the pain brought the patient to the clinic. On examination muscular spasms were found over the entire abdomen, with a maximal pain between MacBurney's point and the costal margin. The patient was operated on for acute appendicitis. The cecum to the hepatic flexure was thick and edematous, "like a stiff tube." There were bluish areas between the haustra. The appendices epiploicae were swollen. There was turbid fluid in the abdomen. The appendix was grossly normal. The bowel was exteriorized, and colostomy was performed. At a later date ileotransversostomy was performed, with recovery. Microscopic examination was not done.

HELLSTROM'S CASE, 1919.—A man aged 37 had tenesmus and bloody diarrhea for a short time. The night before admission to the hospital he collapsed with an abdominal pain and vomiting. He was acutely ill, with marked tenderness in both iliac regions and about the navel. The abdomen was explored through an incision in the epigastrium and in the right lower quadrant. The result of the exploration was negative. The patient continued to have pain in the left side and bloody diarrhea. He was reoperated on on the third day after the first operation. The descending pelvic and sigmoid colon were bluish red and thick walled; the mesosigmoid was inflamed. The extent of the lesion made resection inadvisable. The left kidney was explored because of persistent anuria. Death occurred

five days after the onset of the illness. Postmortem examination of the bowel from the splenic flexure down revealed the same picture as that noted at operation. The mesosigmoid and retroperitoneum were edematous. On microscopic examination the mucosa was found to resemble the *état mammellonné* of the stomach, due to the swelling of the wall. The process seemed localized in the submucosa. There was marked edema, with deposition of fibrin and swollen and broken-down cells. Many streptococci and gram-positive bacilli were seen, some in clumps.

BIEDERMANN'S CASE, 1921.—A woman aged 28 was taken with a sudden severe pain, like a labor pain. She did not pass a stool or flatus. The next day the pain localized in the right lower quadrant of the abdomen. She was admitted to the hospital on the second day. The temperature was 38.2 C. (100.7 F.). She was acutely ill, and her abdomen was slightly distended, with some spasm and tenderness in the right lower quadrant. The operation was performed the same day. The entire cecum was found to be acutely inflamed, bluish red and swollen, and the walls were of the consistency of belt leather. Ileocecal resection was performed, with recovery. Pathologic examination showed no break in the mucosa. The submucosa was chiefly involved, being infiltrated with leukocytes, lymphocytes and plasma cells. The mucosa was brownish, glossy and edematous. Bacterial stains were negative.

LEUCHTENBERGER'S CASE, 1923.—A woman aged 50, six months before her present illness, had an attack of jaundice, vomiting and diarrhea. In February 1923 she was again ill with fever and pain in the right side. Jaundice developed, with chills and eventually coma. Examination showed a jaundiced comatose woman with fever. There was dullness at the base of the right lung. Pleural puncture showed yellowish fluid, which contained leukocytes and erythrocytes. The skin of the abdomen was glossy, and the epigastric veins were prominent and tortuous. Ascites was present. There was pain on deep pressure in the right side of the abdomen, which was not localized. A blood culture was positive for pneumococci. The stool was acholic. The patient died fifteen hours after admission to the hospital. According to the report of the autopsy, the entire large bowel was relaxed, heavy and shapeless. The mucosal folds were changed into thick gelatinous protrusions. The wall was enormously thickened and brawny. Histologic investigation showed that the process involved chiefly submucosa. *Pneumococcus lanceolatus* was recovered from tissue in the culture and was demonstrated in section. The postmortem diagnosis was Laënnec's cirrhosis, gastritis and chronic catarrhal enterocolitis, pseudomelanosis, beginning phlegmon of the cecum and the ascending colon, paranephritic abscess on the right, abscess of the adrenal gland on the right, partly purulent ascites, calculus of the common bile duct, icterus and partial atelectasis.

SAUER'S CASE, 1923.—A boy aged 16 for seven days had pain in the right lower quadrant of the abdomen and fever and vomiting, with normal bowel movements. On admission to the hospital he was acutely ill, with a dry and coated tongue but a normal temperature. There was slight distention of the upper part of the abdomen. At operation the cecum as far as the hepatic flexure was found to be blue-red, swollen and edematous and covered with a fibrinopurulent exudate. Ileocecal resection was performed. Death occurred the following day. On pathologic examination the appendix was not remarkable. The serosa of the cecum was found to be covered with fibrin. There were walnut-like projection of mucosa into the lumen, which admitted about one finger. There was marked infiltration of all coats with leukocytes, which was most marked in the submucosa. Tricocephala were found in the mucosa, but there was no evidence of penetration into the deeper layers.

FENKNER'S CASE, 1925.—Robert M. was admitted to the hospital because of appendicitis, with severe pain and vomiting and a temperature of 38 C. (100 F.). The point of tenderness was very high in the region of the gallbladder. The patient requested immediate operation because of the pain. The appendix was free from inflammation as was the cecum, though the latter showed the veil-like signs of an old process. "The entire transverse colon was in a freshly inflamed condition such as I have previously described, that is, covered by a fresh, red, brawny membrane."

TEUTSCHLAENDER AND VALENTIN'S CASE, 1925.—A woman aged 51 had typhus at the age of 35. Eight days before admission to the hospital she had headache, fever and fatigue. There were no gastro-intestinal symptoms until the day of admission, when there was severe pain in the right lower quadrant of the abdomen, but no vomiting. The patient's condition was diagnosed as acute appendicitis and she was hospitalized. In the right lower quadrant of the abdomen at MacBurney's point and toward the crest of the ileum there was a broad and very sensitive area of resistance, about the width of a hand. A diagnosis of an inflammatory lesion in the cecum was made. Appendicitis was considered improbable. A pararectal incision was made. The omentum was found to be lightly injected. On the contrary, the cecum at the junction of the ileum was brawny and edematous. Ileocecal resection was performed. The mucosa was loosely attached but macroscopically was uninvolved. The submucosa was chiefly involved. According to the record the condition was phlegmon of the individual coats of the cecum around the junction of the ileum, which had not spread widely.

BUNDSCHUH AND WOLFF'S CASE, 1925.—A woman aged 31 for two days had pain in the lower part of the abdomen, with nausea. Her condition was diagnosed as acute appendicitis, and she was admitted to the hospital. The right lower abdominal quadrant was spastic and painful. The temperature was 38 C. The cecum was swollen, red and edematous, extending for about 6 cm. toward the ascending colon without a very sharp border. To a lesser extent, from 2 to 3 cm. of the ileum and the appendix were also involved. Ileocecal resection was performed, with recovery. The pathologic diagnosis was phlegmon of the cecum.

DOBERAUER'S CASE, 1926.—During an attack of erysipelas, Doberauer had severe pain in the right side of the abdomen. A diagnosis of mesenteric thrombosis was made. At operation the cecum and the ascending colon and one half of the transverse colon were found to be very red and succulent, with an extremely edematous wall. Cecostomy was performed. When an attempt was made to close the cecostomy opening, peritonitis developed, but the patient eventually recovered.

MOLL'S CASE, 1926.—A youth aged 21 for nine months before admission to the hospital had had occasional abdominal pain and for four days before, severe pain, diarrhea and vomiting. He showed the hippocratic facies, a boardlike condition of the abdomen on the right side and a temperature of 38 C. The maximum tenderness was in the right lower quadrant. At operation the cecum and terminal portion of the ileum were found to be inflamed and thickened and covered with fibrinous exudate. The appendix was involved to a lesser degree. Ileocecal resection was performed, with recovery. The mucosa of the specimen resembled tuberculous ulceration. The histologic diagnosis was phlegmon of the cecum.

MOLL'S CASE, 1926.—A man aged 30 complained of abdominal pain for a number of days. There was spasm of the entire right rectus muscle and marked tenderness over MacBurney's point. At operation the cecum was found to be inflamed and hard. One area was somewhat soft and was covered with fibrinous

exudate. The mesentery was inflamed. Ileocecal resection was performed, with recovery. The specimen when cut showed an ulcer resembling a peptic ulcer, underlying the exudate. There was no evidence of cancer or tuberculosis. (Note by Moll: Through error the ulcer was not studied further.)

FENKNER'S CASE, 1927.—In this case a clinical diagnosis of appendicitis was made. At operation the appendix was found to be slightly reddened. The cecum for from 8 to 10 cm. was deep red, stiff and swollen and covered with inflammatory exudate. Recovery followed without further operation.

FENKNER'S CASE, 1927.—The patient in this case suffered from severe pain and vomiting and had a temperature of 38 C. The pain was high, almost in the region of the gallbladder. A diagnosis of appendicitis was made. At operation the appendix and cecum were found to be normal. All the intestines were in the pelvis and were adherent, with a fresh exudate. There was free pus in the pelvis. There was an inflammatory process in the sigmoid colon, as in the cases previously described. The pelvis was drained with a glass tube. Three days later a fecal fistula developed 10 cm. from the anus. Cecostomy was performed later. An abscess developed about the sigmoid colon. Recovery occurred after closure of the fistula and the cecostomy opening.

FENKNER'S CASE, 1927.—In this case the patient's condition was diagnosed as acute appendicitis. At operation the appendix was found to be normal. The cecum was red and swollen, and there was an edematous area the size of a quarter above its base. Appendectomy was performed, and cure resulted.

FENKNER'S CASE.—This case is similar to the preceding one. Local resection of the involved area was performed. The wall was 1 cm. thick; the mucosa was intact. The remainder of the wall was phlegmonous and necrotic. The appendix was normal.

OTTO'S CASE, 1927.—A man aged 28 was admitted to the hospital with a fecal fistula and an appendectomy scar. The report from the first surgeon showed that the patient had been admitted to the hospital with a complaint of severe pain radiating upward from the navel and signs of acute appendicitis. Operation was performed on Nov. 11, 1922, at which time the cecum was found to be long and mobile, and markedly inflamed, with fibrinous exudate on the serosa for half the length of the cecum. Appendectomy was performed approximately two years later. An abscess in this region was opened on May 5, 1926 (Otto). The fistula was repaired but broke down six days later. At the second operation the cecum was found to be as thick as a finger and covered with adhesions. Ileocolostomy and later ileocecal resection were performed. The specimen presented a picture of the end-result of a chronic inflammatory process.

FENKNER'S CASE, 1928.—A boy aged 12 had a tonsillar abscess, thrombosis of the corpora cavernosa penis, and thrombosis of both legs. After recovery there was sudden pain in the abdomen, with vomiting and prostration. There was a tumor in the right side, with spasm of the right rectus muscle. At operation the appendix was found to be normal. There was an invagination of the cecum 5 cm. from its origin to the transverse colon. Evagination was done. Three haustra were inflamed, bluish red and inverted. Two were restored to normal shape, but the third could not be so restored. Ileocecal resection was done, with recovery. The mucosa was normal, but there was a phlegmon in all other coats. The pathologic diagnosis (Breslau) was invagination on the basis of an inflammatory lesion of the cecum.

FINSTERER'S CASE, 1931.—A woman aged 29 for four months had fever, cramps and diarrhea, with a loss in weight of 38 Kg. There was a sausage-shaped tumor

in the right lower quadrant of the abdomen. The patient was operated on for ileocecal tuberculosis. Ileocecal resection was performed, with recovery. The pathologist, Paltouf, assumed that an acute phlegmonous process was present in the colon.

BSTEK'S CASE, 1932.—A man aged 22 had an attack of severe pain in the right lower quadrant of the abdomen and since then discomfort after each meal. Neither nausea nor fever was present. There was pain with defecation. A hard tumor the size of an apple was palpable in the right lower quadrant. Roentgen examination showed ulcerative induration of the wall of the cecum. The patient was observed for four weeks, during which time there were two ileus-like attacks. A diagnosis of ileocecal tuberculosis was made. At operation the cecum and the appendix were found to be markedly reddened, covered with fibrinous exudate and fixed to the retroperitoneum. Ileocecal resection was performed, with recovery. Histologic examination showed a small abscess in the submucosa near the origin of the appendix. All coats of the cecum showed marked inflammatory reaction with many leukocytes. Many gram-positive cocci were found throughout the sections.

BSTEK'S CASE, 1932.—A man aged 55 for months lost weight and appetite. For two weeks before admission to the hospital he did not have a bowel movement and suffered from marked distention. For the last three days he had cramplike pains throughout the abdomen, with nausea and belching. The abdomen was distended, with slight spasm and tenderness, which was more marked in the cecal region. The diagnosis was carcinoma. At operation the cecum was found to be distended, with severe changes in the wall. The serosa was bright red and covered with fibrinous exudate. There were occasional tears in the serosa. The ascending colon was free. The appendix was normal except for old adhesions. The cecum was exteriorized and opened by means of cautery two days later. Death followed. Postmortem examination showed a severe necrotizing inflammation of the cecum, with brawny edema of the mucosa and circumscribed fibrinopurulent peritonitis on the serosa.

BSTEK'S CASE, 1932.—A woman aged 45 had a febrile angina. Seven days later there was marked pain in the right lower quadrant of the abdomen with vomiting, prostration and mild diarrhea. Examination revealed healing tonsillitis and diffuse bronchitis. The abdomen was somewhat distended. There was a high fever. A diagnosis was made of perityphlitic abscess. At operation the cecum was found to be adherent to the omentum and the anterior peritoneum. The appendix was embedded in the wall of the cecum. Appendectomy was not done. A tampon was placed to the affected area. The patient died. Postmortem examination showed the cecum to be thick walled and covered with fibrinopurulent exudate. On section the layers were clearly defined. The mucosa protruded and was covered with exudate. There was no evidence of trauma to the mucosa. The ileum was similarly involved in the region of the ileocecal valve. The appendix was uninvolved except in the serous layer. The cecum was involved for 10 cm. On histologic examination the submucosa and the mucosa were found to be tremendously edematous, the muscularis being the least involved. Few pus cells were seen. Colon bacilli were recovered from the bowel and colon bacilli and streptococci from the tonsils.

SZABÓ'S CASE, 1934.—A woman aged 41 a few weeks before admission to the hospital had severe pain in the region of the appendix. The pain disappeared after a time, and a tumor was felt. On admission, she showed pallor and emaciation. There was a mass in the right lumbar region the size of two fists, which was

mobile to respirations. There was also a mass in the region of the appendix the size of an apple, which moved with the first mass. The temperature was 38 C. There was leukocytosis. A roentgenogram showed the cecum to be compressed from without. An operation was performed in view of a diagnosis of disease of the gallbladder and appendicitis. The cecum was found buried in adhesions. It was thick walled, deep red and covered with a fibrinopurulent exudate. The appendix was involved to a minor degree. Ileocecal resection was performed, with recovery. The mucosa was somewhat injected. A few specimens of *Oxyuris* were present. Histologic examination showed the submucosa to be infiltrated with purulent material to a greater degree than the other coats. *Oxyuris* was present only on the surface of the mucosa.

DEMEL'S CASE, 1932.—A man aged 58 seven months before operation had pain in the left side of the abdomen, distention and a loss of 36 Kg. in weight. No blood or mucus was found in the stool. Roentgenograms showed a marked change in the wall of the sigmoid colon, which for about 5 cm. had become an irregular, stiff channel with a lumen the size of a finger. At operation a tumor was found in the sigmoid colon adherent to the lateral peritoneum and mesocolon, which produced stenosis. Exteriorization with subsequent resection was performed. The pathologic report (Morisch) stated that the picture was that of a phlegmonous inflammation of the large intestine. The patient recovered after the closure of a preternatural anus.

KONJETZNY'S CASE, 1935.—A woman aged 32 had a sudden pain in the right side of the abdomen and bloody diarrhea later in the same day. Hot compresses gave occasional relief. She was admitted to the hospital on the sixth day in poor condition. There was an old scar on the right side of the abdomen. Operation was performed for carcinoma of the sigmoid colon. The sigmoid and descending colon were covered by dense adhesions and were very thick walled. A Mikulicz resection was performed, with recovery. The pathologic examination revealed the picture of a phlegmon in a stage of regression.

AUTHOR'S CASE

A girl aged 18 four days before admission to the hospital began to have pain around the umbilicus and in the right lower quadrant of the abdomen. The pain gradually increased in severity but was somewhat alleviated by walking. There was no nausea or vomiting. Administration of a cathartic the day before hospitalization resulted in many loose bowel movements the following day. On the patient's admission to the Buffalo City Hospital the temperature was 100 F. and the pulse rate 84. The patient was well developed and well nourished and did not appear acutely ill. Pathologic changes were limited to the abdomen. There was no distention or spasm but marked tenderness over the right lower quadrant. There was some tenderness on palpation of the right fornix of the vagina.

There was an occasional red blood cell in the urine. There was a leukocyte count of 13,300, with 70 per cent polymorphonuclear leukocytes. A diagnosis of acute appendicitis was made.

A lower right rectus incision was made with the patient under spinal anesthesia. When the peritoneal cavity was opened no free fluid was found. The omentum presented into the wound. Palpation revealed what was thought to be a thickened retrocecal appendix. When the omentum was brushed away, a portion of it was intimately adherent to the cecum about 1 inch (2.5 cm.) above the ileocecal valve. This was left in place and cut free from the remaining omentum after double ligature. It was then seen that the supposed retrocecal appendix was, in fact, a

portion of the wall of the cecum. The cecum for about 3 inches (7.6 cm.) proximately was angry red, its serosa was rough and shaggy and its walls were markedly swollen and edematous. The remainder of the colon was normal in appearance. There was definite demarcation between the normal and the pathologic bowel. The appendix was uniformly fiery red and somewhat edematous. Its serosa was smooth and glistening, and it was nowhere adherent. The area underlying the omental adhesion on the cecum reminded one of the outline of a peptic ulcer. At the time of operation I was not acquainted with the subject of cecal phlegmon, and in view of the fact that the involved bowel did not seem to be tuberculous or carcinomatous and did seem to be an acute inflammatory process, ileocecal resection was not performed. Appendectomy was performed. The omentum was wrapped around the inflamed bowel, and the incision was closed in layers without drainage. At the time the postoperative diagnosis was acute perityphlitis and acute periappendicitis. Convalescence was uneventful, and on the eighth postoperative day the patient was discharged.

Histologic Examination (Dr. Jacobs).—The material as received consisted of an appendix with attached meso-appendix. It measured 7 cm. in length and 0.5 cm. in diameter. There was definite congestion of the serosa; otherwise the material did not appear remarkable.

Microscopically the serosa was found not only markedly congested but diffusely edematous. In the stroma there were numerous interstitial hemorrhages with scattered leukocytes. The vessels were engorged, and the intima was swollen. There were patches of edema and vacuolation in the inner circular layer of muscle. The germinal centers were large, and the rim of lymphocytes was thin and small. In the submucosa there was some adipose tissue. There were some desquamated mucosal cells mixed with cellular debris free in the lumen.

Bacteriologic cultures were not made. Sections were stained for bacteria by the methods of Gram and Giemsa. The serosa was carefully scrutinized for bacteria, and a few scattered gram-positive cocci, paired and in short chains, were found. Examination from the inside revealed a mixed bacterial flora in the debris among which gram-positive cocci in pairs and short chains could be readily picked up. Careful search, however, did not reveal any in the submucosa or in the muscle layers. This case shows more definitely a picture of acute periappendicitis, such as is frequently found in association with an inflammation of a contiguous structure.

PATHOLOGIC ANATOMY

The descriptions of the gross appearance of the acute lesions are strikingly similar. Demel's description is particularly apt: "Das befallene Darmstück sieht graurot bis dunkelblaurot aus, die Serosa ist mit Fibrinbeschlägen belegt, und der Darm selbst fühlt sich hart und teigig an." (The involved portion of the bowel varies from a grayish red to dark bluish red, the serosa is covered with a fibrinous exudate and the bowel itself feels firm and doughy.) The area involved may be a portion of a single haustrum or the entire diameter of the bowel for from 50 to 60 cm. There is, as a rule, a distinct demarcation from normal bowel. The degree of thickening of the intestinal wall is variable and may be so marked as to almost obliterate the lumen. A cross-section shows the reaction to be most marked in the submucosa, which is from ten to twenty times its normal thickness. The amount of swell-

ing in the submucosa sometimes causes a flat papillary protrusion of the mucosa. The mucosa is swollen and glossy and usually intact. Rarely it is ulcerated to a greater or lesser degree. There is edema of the serosa, which is nearly always covered, at least in part, with a shaggy, fibrinopurulent exudate.

HISTOLOGIC STRUCTURE

All layers of the intestinal wall take part in the inflammatory process. As a rule, the mucosa shows the least reaction. The serosa, the muscularis and the submucosa are involved, in the order of increasing severity. The predominant involvement of the submucosa is in keeping with the picture of phlegmon in other portions of the gastro-intestinal tract (Demel, Goldschmidt and Konjetzny). The submucosa is always very edematous. It is densely infiltrated by leukocytes, and there is an increase in lymphocytes and plasma cells. In several cases attention has been drawn to an increase in the proportion of eosinophils. Minute abscesses are sometimes found. The same type of inflammatory reaction is found in the other layers, but in lesser degree. The presence of a fibrinopurulent exudate on the serosal surface has been previously described.

BACTERIOLOGY

In those cases in which cultures have been taken or sections stained for the presence of bacteria, streptococci have been the most frequent invaders. Staphylococci, pneumococci, colon bacilli and putrefactive bacteria have also been demonstrated.

PATHOGENESIS

The portal of entry of infection is thought to be a defect in the mucosa, although this is seldom demonstrable. Fish bones and intestinal parasites have been found in the lumen of the bowel in some instances and have been considered as inciting agents by their discoverers. Fenkner contended that fecal stagnation plays a large rôle, considering infection of the blood stream as possible but unlikely. His experiments with skatole (Fenkner, 1925) are suggestive but do not seem particularly applicable to the disease as found in man. Doberauer, reporting his own case, stated definitely that he believed the phlegmon to be another manifestation of concurrent erysipelas. This seems entirely possible. Bsteh expressed the opinion that the angina which preceded the illness of one of his patients was definitely associated with the lesion in the bowel. The presence of intestinal parasites in the lumen of the bowel and in the mucosa may be significant in those cases in which it was reported (Sprengel; Teutschlaender and Valentin), but the lack of evidence of penetration beyond the mucosa weakens this point of view. The state-

ments of Sprengel and of Finsterer to the effect that the disease is definitely and necessarily associated with acute appendicitis have been thoroughly disproved. In all of the cases previously cited the appendix was uninvolved or involved secondarily by contiguity. It is true, however, that in many of the cases described in the literature as instances of phlegmon of the cecum the condition has been associated with perforative appendicitis.

DIAGNOSIS

As yet the disease has not been diagnosed preoperatively; in fact, the correct diagnosis was made by the pathologist as a rule. Acute appendicitis, carcinoma and tuberculosis have been the most common preoperative diagnoses. The symptomatology is extremely varied. Abdominal pain, usually referred to the overlying quadrant, was the symptom most consistently present. Fever was not remarkable. Constipation was common and diarrhea rare. A tumor was frequently present. Blood, pus or mucus in the stool was not a common finding. The leukocyte count was rarely mentioned. If the possibility of its occurrence is kept in mind, the diagnosis of phlegmon of the colon may on a fortuitous occasion be made preoperatively.

THERAPY

The treatment has been most frequently one or another of the types of resection. Fenkner, almost alone, has refrained from radical surgical measures, aside from the diagnostic laparotomy. In Doberauer's case cecostomy was performed, and in my case, appendectomy. It is my feeling that the treatment is of necessity surgical, because of the extreme uncertainty of diagnosis, both of the disease and of its severity. After a diagnosis has been made, the consideration of radical versus conservative treatment must be faced. It is true that Fenkner's mortality rate with simple exploration, with or without appendectomy, is by far the lowest of the reported series, but it is difficult to determine whether or not the lesions were of comparable severity. In the future I shall be inclined to do resection only in the presence of a predetermined stenosis. It is likely that a short-circuiting anastomosis would be as effective and probably less dangerous. It is well within the realm of possibility that the healing process without resection will cause sufficient scarring to require future resection or anastomosis to overcome obstruction. Anschutz and Konjetzny also are of this opinion.

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A REVIEW OF UROLOGIC SURGERY

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(Concluded from page 564)

BLADDER

Tumor.—Wishard, Hamer and Mertz³⁷ stated that the malignancy of tumors of the bladder can be graded 1 in about 30 per cent of such cases. The most common type of growth on this organ is that which is on a broad, sessile, infiltrating base. A few vigorous endoscopic treatments have been found to give the best results if the tumor is not too large or too broad at the base. Suprapubic resection and electrocoagulation should be employed only if subsequent cystoscopy indicates that progress is unsatisfactory and provided the tumor is in a resectable region. With the modern prostatic electrotome, large masses of neoplastic tissue, which formerly required open operation, can be removed from the bladder. Open operations which necessitated massive electrocoagulation and application of radium were performed by the authors in about 30 per cent of cases of tumor of the bladder. Fifty per cent of the patients who had an open operation and destruction of the neoplasm

37. Wishard, W. N., Jr.; Hamer, H. G., and Mertz, H. O.: An Evaluation of Various Methods of Treating Tumors of the Bladder, *J. Urol.* **35**:503-506 (May) 1936.

with diathermy died within six months thereafter. Radium emanations have been used in approximately 10 per cent of the cases of vesical tumor. The grading of these tumors has varied from 1 to 4, and the size, from small growths, which were treated endoscopically, to large ones, which were treated by open operation. In 75 per cent of the cases in which radium was used, there were recurrences; in the remaining 25 per cent, the application of electrocoagulation alone would probably have given as satisfactory results. The inaccuracy of methods of application through the cystoscope has been the chief difficulty in the use of radium emanations. Applicators available for use through a suprapubic incision are more accurate.

Rabson³⁸ reported a case of leukoplakia and carcinoma of the urinary bladder, which supplements the reports of 125 cases of leukoplakia which have been published. Only 19 of these cases were associated with carcinoma and only 1 with sarcoma. Of these cases of uncomplicated leukoplakia in which age and sex were stated, 57 were in males and 14 in females. The maximal number of cases in the male occurred during the third decade and in females a decade later. Leukoplakia of the bladder was more common than elsewhere in the urinary tract.

The occurrence of cystitis with leukoplakia of the urinary bladder is emphasized by almost all authors, although in some cases it was definitely stated that cystitis was not present. Cystitis was stated to be present in 63 cases. Vesical calculus was reported in 12 cases. Comparison of the small number of cases of leukoplakia associated with calculi (14 per cent) to the number of persons with stones in the bladder diminishes the significance of the etiologic part played by stone as a cause of leukoplakia. There was a history of gonorrhea in only 10 cases. Syphilis was noted in 11 instances. Tuberculosis of the urinary tract was reported in only 1 case in which leukoplakia of the bladder was present.

Carcinoma associated with leukoplakia begins, according to the literature, about a decade after uncomplicated leukoplakia and reaches its height about two decades later. The base of the bladder, including the trigon and neck, was the most common site for leukoplakia. That area was mentioned in 19 cases as being the only portion of the bladder involved, or at least one of the areas included in the process. The right lateral wall was involved in 11 cases, the entire bladder in 9 cases and the anterior and posterior walls in 8 cases each. The superior wall was involved in 6 and the left lateral wall in 5 cases. The trigon was reported to be the most common site for epithelial neoplasms as well

38. Rabson, S. M.: Leukoplakia and Carcinoma of the Urinary Bladder. Report of a Case with a Review of the Literature. *J Urol* 35:321-341 (March) 1936

In many of the cases reported, leukoplakia of the bladder was discovered at necropsy. In others, the patients died soon after the diagnosis was established or after operation.

Infection with Trichomonas.—Heckel³⁹ reported a study of the pathologic alterations in the female bladder and urethra that resulted from infection with *Trichomonas vaginalis*. Of the 43 females with this condition, the youngest patient was 17 and the oldest was 61 years of age. Twelve patients were single, and 31 were married. Eleven (25.5 per cent) of the total number of patients had had a miscarriage. Thirty-seven patients had had urinary symptoms at some time, and in many cases the acute urinary and gynecological symptoms had begun at the same time. In the cases in which urinary difficulties were present, cystoscopy revealed lesions of the bladder or urethra in 24 but did not disclose any abnormality in the remaining 13.

The gynecological symptoms noted were leukorrhea or vaginal discharge in 42 cases, abdominal pain in 14, backache in 12, metrorrhagia in 11, dysmenorrhea in 6 and itching in the region of the urethra in 11. Examination of the vagina revealed a "strawberry" appearance in 12 cases, senile changes in 2, acute vaginitis in 3 and bartholinian abscess in 2. The external orifice of the urethra usually will be found to be normal. In some cases pressure on the urethra will express a discharge, which will be found to contain *Trichomonas*. Cystoscopy will reveal that the pathologic changes in the bladder are limited almost entirely to its base, usually in the region of, and anterior to, the trigon. The following changes may be observed in the urethra: The internal orifice of the urethra, usually from 4 to 8 o'clock if visualized as the dial of a clock, is rough, boggy and gray; it may bleed easily. The mucous membrane of the urethra itself is in folds, which contain many small red patches.

Pieces of tissue were removed from the base of the bladder for biopsy, and sections were made. Marked change in the character of the epithelium was noted. Instead of the usual pseudocolumnar type of epithelium, part of each section was composed of large squamous epithelial cells which were closely packed together. At the surface, the mucosa was relatively normal in appearance, although there were some papillary protrusions near the surface. The sections in most instances were nodular, as if they represented the tops of superficial papillary projections. Analysis of catheterized specimens of urine revealed pyuria in 9 cases and hematuria in 6. In only 2 cases was *Trichomonas* found in the urine; urinary culture revealed streptococci in 9 cases. The diagnosis was based on the history, the demonstration of *T. vaginalis* in

39. Heckel, N. J.: A Study of the Pathologic Alterations in the Female Bladder and Urethra Resulting from Infection with *Trichomonas Vaginalis*, *J. Urol.* 35:520-523 (May) 1936.

the sections from the vagina or urethra and the discovery of the lesions in the bladder or urethra. The differential diagnosis of this condition and other urinary diseases may at times be difficult; usually, if the cystoscopic picture reveals the findings which have been described, the diagnosis can be made, even if *Trichomonas vaginalis* cannot be recovered from the vaginal section at the first examination.

Neurogenic Dysfunction.—Creedy⁴⁰ stated that in most cases neurogenic dysfunction of the bladder is due to sensory lesions. Early in their course partial retention develops, which can often be relieved by rest of the bladder with the inlying catheter, supplemented by the administration of drugs to increase the expulsive force, provided the patient is trained to urinate at regular intervals. Later, the wall of the bladder is injured by the distention, so that some degree of atrophy occurs, and overflow incontinence follows. In selected cases, from six to twelve weeks of rest of the bladder by cystostomy, followed by careful training, may give relief. Regular urination must be maintained permanently if recurrence is to be avoided. With more severe injury to the detrusor muscles, cystostomy is preferably supplemented by presacral neurectomy, which should be regarded only as a means of increasing expulsive force. If the lesion of the nervous system is advanced enough to produce incontinence of the bowels, the prospect of cure by these methods is unfavorable, because sensation is insufficient to permit continuous voluntary contraction of the external sphincter.

Resection of the Neck of the Bladder.—May⁴¹ described a case of sclerosis of the neck of the bladder of a woman aged 65 years; the condition was cured by transurethral resection.

PROSTATE GLAND

Hypertrophy.—Orr and Rue,⁴² in a review of information obtained by a questionnaire concerning cases of prostatic obstruction, found that 73 surgeons had performed prostatic resections 14,104 times and prostatectomy 5,062 times during the same period of time. These totals reveal that resection is performed almost three times as often as is prostatectomy. There were also 214 operations on the neck of the bladder performed with Young's punch or similar punch instruments.

The total number of deaths following resection was reported to be 370, or 2.5 per cent, and from prostatectomy, 195, or 3.8 per cent.

40. Creedy, C. D.: Treatment of the Overflow Incontinence of Neurogenic Vesical Dysfunction, *J. Urol.* **35**:507-514 (May) 1936.

41. May, Ferdinand: Ein Fall von Sphinctersklerose bei der Frau. *Ztschr. f. urol. Chir. u. Gynäk.* **42**:308-311 (Aug.) 1936.

42. Orr, L. M., II, and Rue, D. T.: Present Day Conceptions in the Management of Prostatic Obstruction, *J. Florida M. A.* **22**:573-578 (June) 1936.

There were 107 severe primary hemorrhages accompanying resection which necessitated opening the bladder. There were 164 secondary hemorrhages that required fulguration of the bleeding points, 116 that required transfusion and 54 that required both measures. Six hundred and forty-eight severe infections, or 4.9 per cent of all cases, were reported associated with resection.

Forty surgeons reserved the transurethral procedure for small glands only. Thirty-two employed it in all types of hypertrophy. Secondary resection was necessary 488 times because insufficient tissue was removed at the first operation. Not a single instance of regrowth of tissue was mentioned as a cause for the second resection. One hundred and five patients had had troublesome incontinence, both temporary and permanent. Subsequently, prostatectomy was performed on 172 patients on whom resection previously had been done, and this figure would probably be considerably higher if all patients on whom resections were performed could be accurately traced.

In almost every instance the men performing the largest number of resections were having the best results and recommended the operation for practically all types of prostatic obstruction. The majority recommended that the procedure be used only in carefully selected cases and limited it to the smaller atrophic glands and median bars and for use as a palliative measure in cases of malignant growth.

These results are convincing enough to show that transurethral prostatic resection is an operation of great usefulness and of tremendous value to the patient at the hands of a surgeon with sufficient experience and ability to make proper use of the instruments and equipment that have been placed at his disposal.

Thompson,⁴³ in a review of transurethral surgery at the Mayo clinic during 1935, emphasized the value of intravenous anesthesia by means of pentothal sodium,⁴⁴ which was used for 428 of 1,521 patients who were subjected to various transurethral procedures. This type of anesthesia was used especially for cystoscopic examinations which necessitated general anesthesia, manipulation of ureteral stones and removal of vesical tumors and for urethral dilations and other transurethral manipulations which could be completed satisfactorily within approximately thirty minutes. This anesthesia was also employed in a number of cases of prostatic resection when it was necessary to remove only a relatively small amount of tissue. The broad scope of the transurethral treatment of tumor of the bladder is considered. In 63 cases a tumor

43. Thompson, G. J.: Transurethral Surgery in 1935, *Proc. Staff Meet., Mayo Clin.* **11**:360-363 (June 3) 1936.

44. The chemical equivalent for pentothal sodium is sodium ethyl 1-methyl butyl thiobarbituric acid. This drug has not been accepted by the Council on Pharmacy and Chemistry of the American Medical Association.

of the bladder was removed with an operating cystoscope or was excised with the Stern-McCarthy electroresectoscope. Almost any pedunculated tumor can be removed completely at one sitting. A tumor which infiltrates the vesical musculature is, as a rule, not suitable for transurethral treatment and is approached suprapubically. Radon emanation seeds are frequently implanted transurethrally into a tumor of this type. Thirty-three patients were subjected to 39 attempts to remove calculi from a ureter. In 25 of these cases the stone was removed at the time of manipulation; the Council stone extractor was used in most instances. The author stressed the necessity for great care in the use of this instrument. In 5 additional cases the calculus passed within a few days or a week after manipulation. In 3 cases manipulation failed; in 2 of these the calculus was removed by ureterolithotomy. Transurethral manipulation was therefore successful in more than 90 per cent of the cases. On 695 patients, transurethral prostatic resection was performed 765 times. Study revealed the average age of the patients to be greater than that of patients formerly subjected to suprapubic or perineal prostatectomy. Another point of interest was the fact that in only 7 of these cases was preliminary suprapubic cystostomy performed at the clinic. In 11 other cases this operation had been done previously elsewhere. Thus, only 2.6 per cent of the 695 patients were subjected to preliminary suprapubic drainage of the bladder. In 65 per cent of the cases there was no preliminary preparation involving the use of an inlying catheter, and in many of the remaining cases preoperative preparation lasted only a few days. The presence of pyuria in itself is not necessarily considered an indication for preoperative treatment. If renal function is poor, as evidenced by a value for blood urea of more than 150 mg. per hundred cubic centimeters, operation should be postponed, although several patients whose urea stabilized only slightly below this level and who excreted a large volume of urine daily were subjected to prostatic resection without fatality. The average postoperative stay in the hospital for the entire group was eight and three-tenths days.

Forty-two of the 695 patients had been subjected to prostatic resection in preceding years. In 15 of these cases a malignant tumor of the prostate gland was present, and therefore recurrence might be expected. In the other 27 there was benign hypertrophy. Of an original group of 2,347 patients subjected to transurethral resection, the percentage of reoperation to date, for both benign and malignant hypertrophy, is approximately 3.8. The simplicity and safety of transurethral resection urges repetition of the procedure on both patient and physician if the functional result is not entirely satisfactory, whereas this was not equally true when suprapubic prostatectomy was commonly employed. There was no death among any of the 1,521 patients subjected to transurethral

procedures except in the group of 695 patients who underwent transurethral prostatic resection. Of this group, 7 died, a mortality of approximately 1 per cent.

Rubritius⁴⁵ discussed the question of transurethral prostatic resection and surgical enucleation. He stated that the urologists should not be divided into two groups, namely, those performing resection and those performing prostatectomy. Every urologist must be capable of carrying out both methods.

Rubritius considered transurethral resection with reference to five groups of conditions.

1. In cases of stricture of the urethra the urethral tissues are usually infected. It is evident that when an internal urethrotomy is done in these cases, infection may enter the blood stream. One of Rubritius' patients died of abscess of the brain after internal urethrotomy. Since then he has not performed this operation. He expressed the belief that surgical resection of the urethra is the best method of treating short traumatic strictures that cannot be improved by the use of bougies. When the stricture is impermeable, he performs suprapubic drainage. Commonly a short time after drainage of the bladder, the stricture is permeable and can be dilated with sounds.

2. Rubritius stated that litholapaxy is a satisfactory operation but that it requires skill and practice. Many of the younger urologists have little skill and little practice on account of the rarity of vesical stones. Contraindications against litholapaxy are too large or too hard stones, stones in a vesical diverticulum or stones behind a large adenomatous prostate gland. If a vesical stone and obstruction of the neck of the bladder are present coincidentally, it is necessary to open the bladder and remove the obstruction and the stone at one time instead of performing resection together with litholapaxy. A surgeon not trained in litholapaxy has better results if he removes the stone by the suprapubic route.

3. European urologists are not enthusiastic about transurethral prostatic resection. Rubritius expressed the belief that when urethral and pelvic dilatation are present secondary to adenomatous hypertrophy, only prostatectomy can give complete cure. Transurethral resection, in his opinion, should be reserved for early cases in which there is a small amount of residual urine and in which the urinary disturbances are only mild, and also for cases in which renal function is reduced and the patient cannot endure the strain of a prostatectomy.

4. A papilloma of the bladder is best treated by transurethral methods. Only rarely is the tumor so large that it is necessary to open

45. Rubritius, H.: Die Grenzen transurethraler Operationstechnik, *Ztschr. f. urol. Chir. u. Gynak.* 42:21-30 (Feb.) 1936.

the bladder. Carcinoma is treated by partial resection of the bladder when possible, and if not, by suprapubic incision and coagulation of the growth.

5. The changes in the lower sections of the ureter also may be treated by transurethral methods. It is frequently possible, by cutting the ureteral orifice, to permit a stone in the ureter to pass into the bladder. Too much time must not be lost by conservative methods, thus missing the moment for the operation. Ureterocele may be treated by the transurethral method if it is small. If large, a suprapubic opening is required.

Chute ⁴⁶ reported the case of 2 patients from whom he had removed good sized benign obstructing "regrown" prostate glands in the last few months; his father had successfully performed prostatectomy on these patients ten and eighteen years before, respectively.

The first patient was 59 years old when operated on in 1924. A one stage suprapubic prostatectomy was performed, and three small masses, largely intra-urethral, were enucleated in the usual manner without any difficulty. The microscopist reported that the hypertrophy was benign. Eleven years later the same patient again had acute retention, and a moderate sized benign prostate gland was removed.

The second patient was only 47 years old when operated on in 1916. A one stage prostatectomy was done, from which the patient made a satisfactory convalescence. After the operation the patient was well for almost fifteen years, but in the last three years he had had mild symptoms of recurrent prostatism, a few ounces of residual urine had begun to accumulate and rectal examination revealed a good-sized benign regrowth of the prostate. A two stage suprapubic prostatectomy was performed, the gland, which weighed 50 Gm., being enucleated in one piece.

Twinem ⁴⁷ studied 40 cases of adenomatous hypertrophy of the prostate glands of patients 80 years of age or over. The chief facts in regard to 7 patients within the age group in this report who were treated prior to 1921 were as follows: Five patients were treated surgically, 2 by suprapubic cystotomy, 2 by suprapubic prostatectomy and 1 by a two stage perineal prostatectomy. Four of the patients died.

Thirty-three patients were treated since 1921. The average age in this group was 82.4 years; 8 of the patients were 85 or more. Symptoms of disorder of the prostate gland averaged forty-three months in duration. The longest period of duration was eleven years. Residual urine varied from 4 to 85 ounces (from 120 to 2,550 cc.); 12 patients

46. Chute, Richard: The Recurrence of Benign Obstructing Prostates Years After Prostatectomy. *Tr. New England Branch Am. Urol. A.* 1935, pt. 1, pp. 30-40; *New England J. Med.* **213**:55-57 (July 11) 1935.

47. Twinem, F. P.: The Very Aged Prostatic. *J. Urol.* **35**:349-352 (March) 1936.

had complete retention at the time of admission. The value for urea nitrogen varied from 9 to 55 mg. per hundred cubic centimeters of blood; the average was 25.13 mg. The average three hour excretion of phenolsulfonphthalein in functional tests of the kidneys was 39.4 per cent; the lowest excretion was 19 per cent, and the highest, 69 per cent. The time elapsing between admission and cystostomy varied from a few hours to twenty-one days; the average was approximately four days. Of those patients on whom a two stage prostatectomy was performed, the time elapsing between operations varied from eleven to thirty-four days and averaged twenty-two and three-tenths days. There were 10 deaths. Eight of the patients who died were classified as definitely poor risks, 1 as fair and 1 as good. The patient classed as a good risk was considered neurotic. Six of the 10 patients had definite evidence of cardiac pathologic lesions. One patient had bronchopneumonia on admission, 1 had uremic symptoms and 2 patients had marked chronic bronchitis. In elderly men, when factors are present indicating an unfavorable risk, it is considered advisable in some cases to send the patient home after he has recovered from the cystostomy and allow several months to elapse until he reaches the optimum condition for prostatectomy. If such a patient recovers satisfactorily from the cystostomy and increases in strength during his convalescence, the possibility for a satisfactory result after the second operation is markedly increased. The incidence of cardiovascular disease is high in this group of patients.

The total operative mortality in this series of cases since 1920 was 33.3 per cent. Of the 13 patients who underwent perineal prostatectomy, 3 died, a mortality of 23 per cent. The mortality in the group aged from 80 to 84 years was 24 per cent, whereas in those from 85 to 89 years it was 50 per cent. In a series of 1,049 prostatectomies reported by Young, 31 were performed on patients in this advanced age group, and 5 of these died, a mortality of 16.1 per cent. Three patients were more than 84 years of age, and all of these died. It is interesting to compare the high mortality among these aged patients who had hypertrophy of the prostate gland with the total mortality from prostatectomy regardless of age, which in highly rated urologic departments usually is from 4 to 8 per cent.

Carcinoma.—Hryntsckak⁴⁸ discussed the problem of whether carcinomatous degeneration takes place in hyperplasia of the prostate gland or whether the tumor does not always grow out of the true prostatic

48. Hryntsckak, T.: Die Behandlung des Prostatacarcinoms: Beitrag zur Pathogenese, Histologie und Statistik, Kong. internat. Gesellsch. f. Urol., 1936, pp. 74-81.

gland. This question has given rise to different opinions by different authors. Statistics about the frequency of carcinoma in the hyperplastic tissue differ greatly.

In this study the author has tried, by histologic examination of 310 specimens taken at operation, to approach the solution of the two most important problems, the pathogenesis and the histology of carcinoma of the prostate gland. Apart from the statistics derived from this work about the frequency of carcinoma, he has tried to discover such alterations as might account for the frequency of such a lesion in the prostatic hyperplastic tissue. Furthermore, he has tried to discover the first alterations in the tissue which might lead to carcinoma and to determine their value. For the sake of a better understanding, and on account of the great importance of the subject, as many photomicrographs as possible have been published with the report, as the consecutive alterations of the histologic aspects cannot be illustrated merely by words well enough to convey a uniform appreciation to other investigators.

When examining the microscopic sections, Hryntschak was soon struck by the appearance of foci of regeneration in a great number of cases of hyperplasia. Furthermore, he found out that these centers of regeneration were never lacking in any of the cases in which early carcinoma was present. This fact necessarily attracted attention. The suggestion that these centers of regeneration might stand in some pathogenic connection with development of carcinoma has proved to be fertile in results. Hryntschak expressed the belief that he has been able to prove, through deductions and photomicrographs, that it is possible to establish an uninterrupted chain of intermediate phases between regeneration and carcinoma, giving explanation of the pathogenesis of carcinoma of the prostate.

Regeneration in the true prostatic gland as well as in its hyperplastic parts certainly often develops from an inflammatory process, but it probably often develops also from trauma. Hryntschak's photomicrographs have shown that some of the groups of tubules must have gone through several regenerative processes, caused by constantly repeated lesions, and that all along these constantly repeated cycles of regeneration the morphologic aspect of these groups grow more and more irregular and atypical. Though these centers of regeneration have only been found in specimens taken at operation, it is known from the literature that analogous conditions exist in the true prostatic tissue.

The similarity between the histologic picture of carcinoma of the true prostate tissue and that of carcinoma of the hyperplastic parts of the gland can now be understood.

The centers of regeneration are never to be found in one spot alone but always on several spots of the prostatic hyperplasia, especially in

its peripheral zone. This corresponds to Hryntschak's experience that in most of the cases in which early carcinoma is present the lesion is in the periphery of the enucleated parts. This also explains his observation that in cases of early carcinoma the lesion seems to originate from more than one spot alone; the centers of malignant degeneration originate from different spots.

Another striking morphologic peculiarity of carcinoma of the prostate gland, emphasized by all authors, lies in the diversity of its forms. In the same case one may find in different parts the carcinomatous proliferation at one time as an adenocarcinoma and then again as a medullary, a scirrhous or a squamous cell carcinoma. Several authors have grouped these forms into several types. Hryntschak expressed the opinion, based on his researches, that carcinoma develops from multiple regeneration centers; he added that the malignant proliferations each issue from a separate regeneration focus and present diversities in their structure dependent on the different stages or kinds of regeneration. These individual carcinomatous foci then grow toward each other, penetrate each other and fuse, and in the end present the well known picture of carcinoma of the prostate gland. As he has not yet been able to give proof of this hypothesis, it can serve only as a hypothetical basis for further research.

His researches have proved that carcinomatous degeneration takes place also in the hyperplastic parts of the prostate. Statistics about the frequency of carcinoma in the hyperplastic parts versus its frequency in the true prostate gland reveal that carcinoma occurs almost twice as often in the latter as in the former. On this account, Hryntschak stated that he believes he has found the explanation in his conception of the pathogenesis of carcinoma of the prostate. The prostate gland is frequently and during a long time subjected to irritation leading to repeated regeneration; if carcinoma develops there more frequently than elsewhere, it may be accepted as an indication for the correctness of his suggestion, namely, that there is an etiologic connection between these two different proliferations of the tissues.

The problem of new development of carcinoma many years after prostatectomy may also be explained by these facts.

Blanc⁴⁹ reported that he had recently observed 2 new cases of an exceptional form of carcinoma of the prostate gland, a cystic type; this made a total of 4 cases that had come under his notice. These, together with only 3 similar cases that he had found recorded in the literature, were outlined.

49. Blanc, Henry : La forme kystique du cancer de la prostate, *J. d'urol.* 41: 13-27 (Jan.) 1936

The condition is characterized by the presence of enormous cystic cavities, usually single, occupying one entire lobe of the prostate gland and filled with pure blood, blood serum or serohemorrhagic fluid, possibly mixed with débris from the lesion. The question arises whether or not such a cyst or tumor is primary. In 3 of the cases the view that the carcinoma was primary seemed justified; in the remainder it appeared that giant cysts had been formed by coalescence of multiple small cysts and that at some time during their evolution a neoplastic process had been superimposed. Why such cystic formations are so rare while epithelioma of the prostate is observed so frequently is not known. It is important to note, however, that this cystic process seems to develop solely on the prostate gland itself and not on an adenoma. The growths are primary glandular carcinomas and not adenomas that have become carcinomatous. It is possible that there may have been a simple coexistence of a prostatic epithelioma on the one hand and a prostatic cyst on the other, the latter being produced by neoplastic obliteration of certain glandular acini, without primary intramural hemorrhages but with secondary intracystic bleeding. The cyst would thus be added to the neoplastic process, which would remain clinically masked while continuing to evolve.

The symptoms at first are those of common prostatism, with rectal examination revealing nothing and with the clinical course differing in no respect from that of common epithelioma of the prostate. As time goes on, however, the peculiar aspect of the organ under rectal examination cannot fail to be noted. None of the common signs of epithelioma, namely, hardness, irregular deformity and lack of delimitation, are present. The prostate gland, greatly increased in size, bulges considerably into the rectum, but, contrary to what is observed in prostatic hypertrophy or in neoplasm, the two lobes are absolutely separated by a pronounced median furrow. This tumefaction, which is painless, has a clearly rounded form and a smooth, regular surface. Most striking of all is the elastic and fluctuating consistency, giving the impression of a collection of fluid. At no point of the tumor is there any hardness; the consistency is uniform and the wall so thin that the pressure of a finger-nail might tear it. In Blanc's patients this condition persisted unchanged for several months. In 2 of his cases and in the 1 case of Andre, the cystic masses reappeared after operation.

It is well to bear in mind the possibility of such a cystic form of carcinoma, since in most cases there will be nothing to suggest carcinoma of the prostate, either in the clinical history or on rectal examination. The diagnosis of a cystic tumor is evidently not difficult, and the presence of the characteristic median furrow eliminates the possibility of prostatic hypertrophy. The only difficulty will be in determining the benignity or malignancy of the cystic tumor, and this only

time can reveal. Blanc expressed the belief that one should always suspect the tumor to be malignant and be guarded in prognosis. It is difficult to state with precision the time required for evolution of cystic carcinoma of the prostate, since nothing is known of its beginning and too few cases are as yet on record.

Treatment can only be palliative. If rectal disturbances are severe, measures must necessarily be directed to the cystic formation itself, but if they are only slight, one may hesitate to operate on the cyst itself in view of the frequency of recurrence and the tendency of the tumor to continue its evolution. Measures that may be employed, if necessary, are rectal puncture, rectal incision, transperineal puncture, perineal incision after perineotomy and transvesical drainage. Incision by the perineal route appears to be the first and probably the best method to attempt. If diagnosis were certain, radiotherapy might be tried. Blanc stated that beyond attempts to keep up the patient's general health, the surgeon will have to be content with incision of the cysts by the perineal route and the performance of cystotomy when catheterization has become impossible or has to be done too frequently. He would not hesitate, however, in a new case to make an intraprostatic application of radium after perineal incision. Experience might show that deep radiotherapy is useful in these cases.

Oreja⁵⁰ stated that it is generally admitted that in 20 per cent of all cases prostatic obstruction is of carcinomatous origin; according to recent investigations, however, the proportion may be even higher. The fact that hypertrophy and carcinoma occur together causes the patient to perceive early the troubles peculiar to glandular hypertrophy, which induces him to consult a urologist at a stage of the disease when it may sometimes be admissible to consider the possibility of successful radical intervention.

With regard to the surgical treatment of cancer of the prostate gland, one of two main routes of approach may be chosen when one is proceeding to the radical extirpation of the carcinomatous prostate gland: the perineal or the suprapubic route. From discussions, it is obvious that the perineal route is used more often than the suprapubic route, which suggests that the results obtained by the former method are better. There is only one positive fact which may be recorded, namely, that the best results are obtained when the operation is performed only in cases in which cancer was thought to be present or in such cases in which a diagnosis of benign hypertrophy was made and the existence of the carcinomatous process is realized only in the course of the operation.

50. Oreja, Benigno: Tratamiento del cáncer de la próstata, Kong. internat. Gesellsch. f. Urol., 1936, pp 160-193.

Oreja concluded that in the presence of hypertrophy of the prostate gland in which small, suspicious nodules are perceived by rectal palpation, and with even more reason when the latter present themselves so vaguely that the diagnosis becomes still more doubtful, prostatectomy must be performed. On the other hand, in cases in which carcinoma is diagnosed with certainty, it is preferable not to operate.

Smith⁵¹ stated that symptoms of carcinoma of the prostate gland do not manifest themselves until the neck of the bladder is involved. From 1919 to 1935 he has performed radical perineal prostatectomy after the method described by Young on 50 patients with this lesion of the gland. An analysis of these cases is submitted, and the technic of the operation with its indications and contraindications is considered.

In a large proportion of cases that part of the prostate gland which is palpable by rectum is the first to become malignant. In all but exceptional cases, carcinoma of the gland is of a stony consistency, with a tendency to form in the gland a ridge which has a relatively sharp edge, in contradistinction to the flat induration of inflammation or the symmetrically rounded surface of hypertrophy. In this series of 50 cases the diagnosis was sufficiently definite for the operation to be planned beforehand in 43 cases. In 7 cases the diagnosis was uncertain until the gland was exposed, when a specimen was removed for biopsy and frozen section was made immediately.

The technic of the operation may be briefly described as follows: The gland is exposed through a curved preanal incision. The urethra is opened at the apex of the prostate, and a Markley tractor is inserted. Denonvilliers' fascia is cut across and, by blunt dissection, is stripped off the posterior surface of the gland, thus removing the rectum from the field of operation. The lower half of the seminal vesicles are exposed. Laterally, the gland is practically free in the pelvis. The membranous urethra is cut across, leaving a cuff of urethra projecting from the triangular ligament. The apex of the gland is depressed and by blunt dissection with the handle of a scalpel is freed from the loose tissue anterior to it. This line of cleavage is followed until the anterior wall of the bladder, recognized by its circular fibers, is seen. This is incised, and the incision is carried down on each side of the prostate. The tractor is then removed, and the anterior commissure of the gland is seized with double hooks and drawn forward and downward; this exposes the trigon. The trigonal flap is then pushed upward off the vesicles, which are freed from in front and from behind. The attachments of their tips are clamped with rightangled hemostats and cut across. These clamps control the chief supply of blood of the prostate

51. Smith, G. G.: Total Perineal Prostatectomy for Carcinoma. *J. Urol.* **35**: 610-617 (June) 1936.

gland. The vasa deferentia are cut and tied just above their ampullae, and the vesicles and prostate gland are removed. The central point of the neck of the bladder anteriorly is then sutured to a corresponding point in the stump of the urethra. Two lateral sutures are placed on each side, and the tip of the catheter is inserted into the bladder. The posterior central point of the neck of the bladder is then sutured to a corresponding point in the urethral stump. Cigaret drains are placed to each vesicular bed, and the perineum is closed with catgut and dermal sutures except for the left lower angle of the incision through which the drains are led.

Constriction at the point of union of the urethra and the bladder developed in 6 cases. Dilation was required occasionally, but the condition seemed to be caused by scar tissue outside the urethra rather than by a true stricture. Even the patients who died of recurrence of the disease were unusually free from symptoms of obstruction. Only 2 such patients required suprapubic drainage. The degree of urinary control was excellent in 11 cases, good in 19, fair in 7 and poor in 6, while in 1 case the result was not given. A rectal fistula was present in 1 case. Of those patients with poor control, 1 was suffering from tabes and 1 was feeble-minded. Five of the 50 patients in this series died in the hospital. Twenty-five others died of carcinoma, having lived an average of three years. Six lived more than five years, the longest period being nine and a half years. Three patients lived seven and a half years and were in good health for at least five years after operation. Of the patients who died from the disease, 11 had definite involvement of the vesicles that was noted at the time of operation. Fourteen patients were alive and well at the time of the report. Roentgenograms had not been taken, but all the patients were in good general health and were free from pain, and on rectal examination evidence of recurrence was not noted. The duration of life since the operation was as follows: 2 patients were alive seven years afterward; 2 patients, five years; 5 patients, from four to five years; 2 patients, from three to four years; 1 patient, two years, and 2 patients, less than a year.

TESTIS

Ectopic Testis.—Pace and Cabot⁵² stated that a study of 24 retained testes in adults suggests that there is progressive deterioration as the years go by. Thus a specimen from a patient in the second decade revealed germinal epithelium which might have developed normally. The specimen from the other patient in this decade showed complete

52. Pace, J. M., and Cabot, Hugh: A Histological Study in Twenty-Four Cases of Retained Testes in the Adult, Surg., Gynec. & Obst. **63**:16-22 (July) 1936.

degeneration, and it is not improbable that the testis was undeveloped from the start. All of the 6 specimens from patients in the third decade revealed some degree of atrophy, but all had remaining epithelium which could have gone on to satisfactory development. Four of the 5 specimens from patients in the fourth decade revealed epithelium which might have developed normally. The fifth specimen was extensively atrophied. Two specimens from patients in the fifth decade had epithelium which might have developed, whereas 2 others had gone on to complete destruction. One of these was a testis retained within the abdomen, in which, on theoretical grounds, one would expect more complete atrophy. Both of the specimens from patients in the sixth decade revealed complete fibrosis and destruction. It did not seem reasonable to assume that these could reveal any important degree of regeneration. All of five specimens from patients in the seventh decade revealed extensive degeneration and hyalinization.

It is interesting and, the authors stated, important, to note that in the normal routine examination of these 24 specimens 3 were found which showed evidence of carcinoma. Two of these were from patients in the third decade who had a lesion described as adenocarcinoma. The third was from a patient in the seventh decade who had a lesion which was controversial.

These findings seemed to the authors to strengthen the opinion that the abnormally placed testis is much more likely to have carcinoma than the normally placed testis. It further suggests that rather more careful study of misplaced testes removed at operation or found at necropsy might shed still more light on this question, which is of great importance.

Campbell⁵³ stated that perineal testicular ectopy is an unusual observation. Eccles found 5 cases in 936 instances of undescended testis; Robertson recently reported a case in a boy aged 3 months, who was operated on. There are 99 cases recorded in the literature to date.

The perineal testis is subject to the same unfavorable factors as are organs in inguinal or other forms of maldescent. If the anomalous condition is permitted to persist, atrophy and loss of fertility of the gland are certain. The organ is subjected to ill borne trauma, and according to Dean the improperly descended testis is 200 times more likely to become the site of a malignant growth than is a normally descended gland.

Treatment is necessarily surgical. There is no preventive treatment. Unless the ectopic gland is producing symptoms, operation should be

53. Campbell, M. F.: Perineal Testicle, *J. A. M. A.* 106:2232-2234 (June 7) 1936.

withheld until after the patient's third birthday. It is advisable, however, to transplant the testis to its normal scrotal position soon thereafter. Through an incision from 3 to 4 cm. long, the external inguinal ring and the upper portion of the ectopic spermatic cord are exposed. The incision begins just above the level of the external ring and extends downward in the scrotofemoral fold toward the ectopic gland. Between the superficial and the deep perineal fascial layers the testis will often be found firmly anchored by its gubernaculum. The gubernaculum is divided, so that a generous segment remains for suture to the depth of the new scrotal pocket. The cord, which will be found of ample length, is mobilized to the external inguinal ring and is examined for a hernial sac. The tunica vaginalis is now everted behind the testis. An adequate pocket is made in the scrotum to receive the testis. The pocket is turned inside out, and to its depths the gubernaculum is stitched with fine chromic catgut. Care must be observed that in transplanting the testis to the scrotum the cord is free from torsion. When the testis is properly placed, it is well to close the fascial ring of the upper part of the scrotum with two or three fine chromic catgut sutures to keep the testis down in the scrotum.

Orchitis.—Ohlmacher⁵⁴ stated that orchitis may appear in from two to sixteen days after parotitis and most commonly in from four to eight days. The fever tends to persist for from two to six days and falls by lysis. A rather imposing proportion of atrophy, as high as 60 per cent according to Catrin, is said to occur in the absence of operation, which, briefly, has in the reported cases consisted of making incisions in the tunica albuginea.

Involvement of the ovaries is uncommon. Involvement of either the male or the female gonad is definitely inclined to appear as a late complication. According to Osler, "the orchitis may occur before the parotitis, or in rare instances may be the only manifestation of the infection (orchitis parotidea)." He stated succinctly that "involvement of the ovaries is rare."

Ohlmacher reported a case of unusual orchitis parotidea without parotitis along with an exceptional case of primary oophoritis caused by the virus of mumps.

Tumor.—Smith, Dresser and Mintz⁵⁵ reported 100 cases of tumor of the testis assembled from a number of hospitals around Boston.

Teratomas occurred most frequently in patients between the ages of 20 and 30 years; embryonal carcinoma, in those between 30 and 40

54. Ohlmacher, A. P.: *Orchitis and Oophoritis Parotidea (Osler): Report of Two Cases*, J. A. M. A. **106**:2053-2054 (June 13) 1936.

55. Smith, G. G.; Dresser, Richard, and Mintz, E. R.: *Radiation Treatment of Tumors of the Testicle*, Tr. Western Branch Soc. Am. Urol. A. **4**:48-55, 1935; J. Urol. **34**:462-469 (Nov.) 1935.

years. There was no marked difference in these two groups in the rate of progress of the disease. A definite history of trauma was obtained in 13 per cent of cases; in 5 per cent, the uninvolved testis was or had been incompletely descended. In 3 cases the tumor was bilateral. In 15 per cent of the cases the patients apparently were well two or more years after orchidectomy. Six of these had not been subjected to irradiation. In only one patient in this group was metastasis detected. So far as is known, all patients who had metastasis when irradiation was instituted have died of the disease or still have metastasis. In only 40 per cent of the cases in this series was irradiation adequate. A standard should be established for roentgen therapy after orchidectomy. It is essential to irradiate the entire abdomen, as the most common site for metastasis is in the lumbar chain of lymph nodes. If the thorax is not included in the first series of treatments, diagnostic roentgenograms should be taken every two months for at least two years.

Hinman and Benteen⁵⁶ stated that attempts to ascertain the relationship of cryptorchidism to tumor of the testis have heretofore been based on statistical surveys and that it is difficult to find a more satisfactory method of study for this particular problem. The simultaneous occurrence of cryptorchidism and tumor of the testis has been reported frequently in the past. In different series this association has been noted at 12.2 per cent by Hinman, 15 per cent by Scott, 11.7 per cent by Chevassu, 13.5 per cent by Dean and 11 per cent by Rubaschow. Of 57 consecutive, histologically verified cases of tumor of the testis in the London Hospital, 15.9 per cent occurred in cases in which there was inguinal maldescent of the testis. In Hinman and Benteen's series of 40 cases of primary tumor of the testis, the clinical diagnosis in 39 was verified histologically. From 1913 to June 1, 1935, 39,359 male patients were discharged from the University of California Hospital. During this period a study was made of 155 patients with undescended testes. One of every 253 male patients had an undescended testis. The incidence of primary tumor of the testis was 1 in every 983 patients. Of the 40 primary tumors, 19 were classified as teratoma, 14 as seminoma, 6 as embryonal carcinoma and 1 as an embryoma. Trauma to the scrotum was noted definitely 11 times and questionably twice.

Primary neoplasms of the testis occur more frequently if cryptorchidism is present than if it is not. Whether all undescended testes are potentially malignant is a debatable question. Study of Hinman and Benteen's series showed that in 2 per cent of the patients who had undescended testis a tumor of that organ developed. The incidence of primary neoplasms of the male sex gland in the group in which

56. Hinman, Frank, and Benteen, F. H.: The Relationship of Cryptorchidism to Tumor of the Testis, *J. Urol.* **35**:378-381 (March) 1936.

the testes were descended was 0.09 per cent. The incidence of tumors arising in cases of cryptorchidism is reported as being from 11 to 15 per cent in different series. The group of Hinman and Benteen showed a correlation of 7.5 per cent. In other words, among approximately 40,000 male patients, seen at the University of California Hospital, tumor of the testis occurred 20 times as frequently in undescended testes as in those normally placed.

SPERMATIC CORD

Torsion.—Kinney⁵⁷ reported a case of torsion of the spermatic cord. About 250 cases of torsion have been reported in the literature. Many cases of atrophy of the testis are unquestionably caused by previous torsion. Early diagnosis is imperative, and detorsion can be successfully accomplished in the majority of cases only if the patient is seen within an hour or so after torsion has occurred. Even if detorsion can be performed, atrophy of the testis usually occurs. Torsion of the cord can occur at any age, but most frequently during adolescence. Etiology is of little assistance in the prevention, diagnosis and treatment of torsion. The right spermatic cord and testis as compared to the left are involved in a ratio of about 3:2. The treatment should be surgical, and an appeal is made for prophylactic surgical measures and for the inspection of the opposite side in all cases of torsion of the spermatic cord.

URETHRA

Stricture.—Riba⁵⁸ stated that for the division of urethral strictures he has developed a no. 12 French, semiflexible, insulated electro-urethrotome equipped with an expansible cutting loop. A standard filiform bougie is attached to act as a guide. After the urethrotome has been inserted, the loop may be expanded to the desired caliber just proximal to the deepest stricture. Contact is then made with a foot-switch, and the instrument is withdrawn. The current may be discontinued any time during the withdrawal. All cutting is done at a position corresponding to the figure 12 on the dial of a clock, along the surgical urethral roof and distal to the cut-off muscle. There is no shock and little active bleeding. Urethral anesthesia with a 1 per cent solution of cocaine has been used as a routine in all but 1 case. Patients who have urine in the bladder are able to void immediately after urethrotomy. An indwelling catheter is unnecessary.

A summary of cases of stricture in which electro-urethrotomy was performed is presented in the accompanying table.

57. Kinney, W. H.: Torsion of the Spermatic Cord, Tr. Western Branch Soc. Am. Urol. A. 4:32-38, 1935; J. Urol. 34:470-476 (Nov.) 1935.

58. Riba, L. W.: Electro-Urethrotomy in the Treatment of Urethral Strictures, J. A. M. A. 106:1971-1975 (June 6) 1936.

Urethritis.—Ormond⁵⁹ reported the results with the use of fever therapy in the treatment of gonorrheal urethritis of males at the Henry Ford Hospital. The air-conditioned Kettering hypertherm cabinet was used and was operated by immersing the nude patient, from the neck down, in air at a temperature of from 140 to 160 F. and at a humidity of from 35 to 40 per cent, so that the heat-regulating mechanism of the patient was rendered useless and his temperature increased. This method was used in 21 cases of gonorrheal urethritis which affected 20 patients in the past two years. The patients were divided into four groups. The first 4 patients treated comprised group 1. These patients received from two to four treatments at intervals of from four to eight days; the temperature was raised to 105 or 107 F. and maintained at that level for five hours. Posterior urethritis developed in 1 patient during treatment. A second patient refused treatment after the third dose. Two days later organisms were found in the urethral discharge, and three weeks later acute epididymitis developed. Three months sub-

Follow-Up Notes on Patients with Stricture who were Given Treatment

	Dilation (164 Cases)		Electro Urethrotomy (49 Cases)	
	No	%	No	%
Returned	123	75 00	46	94
Failed to return .	41	25 00	3	6
Improved	97	59 14	46	94
Unimproved .	22	13 42	2	4
Made worse .	2	1 22	0	0
Result unknown .	2	1 22	1	2

sequent to this he did not present any evidence of gonococcic infection. A third patient refused further treatment when organisms were found after the second fever treatment and consulted another physician. The fourth man, a professional football player, received four treatments at weekly intervals; he played football between treatments. Four days after the fourth treatment gonococci were present in the discharge from the urethra. Group 2 consisted of 6 patients on whom the series of treatments was incomplete for various reasons. Group 3 consisted of 5 boys who were between 14 and 16 years of age. These boys were kept in bed, and fluids were forced moderately. They were given a bland diet, making the conditions favorable for obtaining the most satisfactory results. The first boy, who was seen three months after the onset of the urethritis, had only a small amount of discharge, which gave a specific reaction for the gonococcus. He was given one treatment at 107.2 F. for five hours; after this the urethral discharge disappeared. A month later there was no discharge, and the prostatic secretion did

59. Ormond, J. K. Experience with Fever Therapy in the Treatment of Gonorrheal Urethritis, *J. Urol* 35:551-556 (May) 1936

not contain any pus. The second boy, who was seen a month after onset of the disease, had gonorrheal urethritis and ophthalmitis. He received five treatments of five hours each, at intervals of eight days, at a temperature of 107 F. The ophthalmitis disappeared after the first treatment, and the discharge ceased after the fifth treatment. The third patient, who was observed two and a half weeks after the discharge appeared, received five treatments of five hours each, at weekly intervals, at a temperature of 107 F. Seven days after the last treatment gonococci were still present in the discharge from the urethra. Group 4 consisted of ambulatory patients.

In 2 of 15 patients who were ambulatory, complications arose during treatment, but they did not develop in any patient when he was undergoing treatment in the hospital. The treatment usually caused a prompt and striking decrease in the urethral discharge, and in the patients who completed the series the course seemed shorter than it usually is with the ordinary forms of treatment. The favorable effect of the treatment of complications was marked. Arthritis and epididymitis yielded promptly, and in the 1 case of ophthalmitis the condition cleared up after one treatment. While this is a small series of cases from which to draw conclusions, all who have used this form of therapy in these complications report the same results. Temperature as high as 107 F. has in most instances been tolerated well. An interval of three or four days between treatments is preferable, and the duration of a treatment should not exceed six hours. The disadvantages of this method of therapy are that it is somewhat of an ordeal, is expensive, necessitates loss of time from work and makes known the patient's disability. The majority of patients who have acute gonorrheal urethritis are young men with limited incomes who cannot afford to lose time from work. In the cases in which acute lesions were healed, the usual number of treatments was five, and there is no assurance that complications will not arise. The treatment is not free from danger, since death has occurred in the course of a treatment.

Sherman⁶⁰ reported on 400 cases of gonorrhea in males. Two hundred of these patients were treated by instillations of various antiseptic solutions, urinary sedatives, prostatic massage and the usual symptomatic treatment accepted by most physicians. The remaining 200 patients were treated by a combination of antiviral, vaccine and prostatic massage. All other treatment was omitted. The time required to stop the discharge from the urethra and to effect an apparent cure was shortened two and five weeks, respectively, by the use of antiviral solution. No deleterious effects were observed from the prolonged use of this solution. There was no increase in irritation of the urethra, no

60. Sherman, W. L.: Antiviral Treatment of Gonorrhea, *J. Urol.* **35**:546-550 (May) 1936.

burning and smarting on urination, no periurethral thickening and no stricture of the urethra in these cases. The occurrence of complications was 75 per cent less in the patients who were given antiviral than it was in those on whom ordinary treatment was employed. No cases of gonorrheal arthritis were observed. The administration of vaccine in small divided doses, given simultaneously at different sites, seemed to have a beneficial effect over the usual method of single injection.

VERUMONTANUM

Baldrige⁶¹ reported a case of congenital hypertrophy of the verumontanum. The symptoms and pathologic changes in these cases are the same as those which are seen in cases of posterior urethral obstruction from any cause. Symptoms develop early or late, depending on the degree of obstruction and on the degree of compensatory hypertrophy of the musculature above the point of obstruction. Dilatation of the posterior urethra and bladder and extensive bilateral hydro-ureter and hydronephrosis are present. The ureteral valves are incompetent. Symptoms depend on the stage of the disease and on the presence or absence of infection. Those depending on the mechanics of the condition are difficulty in urination, dribbling, frequency and dysuria, but most important of all, intermittent distention in the lower part of the abdomen and paradoxical incontinence. The secondary group of symptoms, caused by renal failure, are those of uremia from any cause.

The author's patient was an 11 year old boy, whose chief complaints were hematuria and pain over the lower part of the abdomen and in both lumbar regions. Physical examination gave negative results except for the abdomen, which revealed extreme tenderness and muscle spasm in the region of the bladder and of both kidneys. There was an abdominal tumor in the midline, which extended from the symphysis pubis to above the umbilicus.

Two weeks after admission, during which time permanent drainage by means of a catheter had been instituted and the patient's urine had become clear of blood, cystoscopy was performed. The wall of the bladder was very thin and not trabeculated; it was generally congested. No diverticula, tumors or foreign bodies were seen. The verumontanum was enormously enlarged and filled the entire undilated portion of the posterior urethra. It protruded into the neck of the bladder and could be pushed from side to side. There were no demonstrable valves. The tumor did not bleed easily. It was destroyed as completely as possible by electrocoagulation, and permanent drainage by means of a catheter was employed.

61. Baldrige, R. R.: A Case of Congenital Hypertrophy of the Verumontanum, *Tr. New England Branch Am. Urol. A.*, 1935, p. 1, pp. 10-18; *New England J. Med.* 213:46-49 (July 11) 1935.

On account of poor tonus of the bladder, the boy was unable to void after coagulation of the verumontanum, so suprapubic drainage was performed. After several weeks of suprapubic drainage, the sinus was allowed to heal and the patient was discharged, voiding normally.

UROGENITAL TUBERCULOSIS

Negley⁶² stated that nephrectomy continues to be the procedure of choice in cases of positive unilateral renal tuberculosis and should be done as early as possible in order to avoid the complications of tuberculous cystitis or epididymitis. The high mortality in cases in which operation is not performed substantiates this dictum. The belief that any operation, cystoscopic manipulations or retrograde pyelograms are likely to induce terminal miliary tuberculosis or fatal toxemia is contrary to facts.

Spinal anesthesia, supplemented by solution of sodium amytal and sodium evipal⁶³ intravenously and the use of opiates, has been preferred by Negley for operations on both the renal tract and the genitalia. The significance of smears for acid-fast bacilli has not been sufficiently emphasized; a few negative smears are too frequently accepted as evidence that a patient is free from tuberculosis. Inoculation of guinea-pigs, as well as cystoscopy, should be carried out in every case in which urinalysis has disclosed the presence of albumin and pus after six negative smears. Every patient who has active tuberculosis should have acid-fast smears made at least once a month. Owing to the apathy of patients and also of the medical profession, the majority of cases of renal tuberculosis are not diagnosed until the late stages. In 400 necropsies on patients who had died from tuberculosis, there were no instances of healed renal tuberculosis. A tuberculin test of the skin has been done on inoculated guinea-pigs at the end of three weeks, and, although sufficient data are not available, it is believed that this will shorten the time required for diagnosis and add to the number of positive findings.

No patient who has tuberculosis of the genitalia should be dismissed without a complete study of the kidneys for possible renal tuberculosis, particularly those in whom urinalysis reveals tubercle bacilli. Vasectomy on the opposite side in tuberculous epididymitis or orchitis is always indicated, owing to the large percentage of cases in which involvement is bilateral (35 per cent). Orchidectomy is not indicated as often as is supposed. If care were exercised in the diagnosis and operative technic in epididymectomy, many testes would be saved.

62. Negley, J. C.: Urogenital Tuberculosis, *J. Urol.* **35**:668-673 (June) 1936.

63. The chemical equivalent for sodium evipal is sodium n-methylcyclohexenylmethylmalonyl urea. Sodium evipal has not been accepted by the Council on Pharmacy and Chemistry of the American Medical Association.

Of 139 cases of tuberculous epididymitis or orchitis, the prostate gland and vesicles were involved in 109 cases (84 per cent) and the kidney in 43 (33 per cent).

Lazarus and Rosenthal⁶⁴ stated that primary tuberculosis of the penis is a rare clinical entity, particularly when it occurs in adults, as only 25 cases (including the authors') have been reported to date. It is usually diagnosed late in its course, since it is most often mistaken for chancroid, chancre or granuloma venereum. The diagnosis can be confirmed only by histologic study and preferably by inoculation of animals.

The disease is characterized by a slowly spreading, painful ulcer with an indurated, bluish-gray border that has a marked tendency to become undermined and by a central ulceration covered with a dirty, yellowish, odorless slough. In the later stages, areas of cheesy necrosis may be seen near the indurated margin, and nodules are found in the region of the base of the ulcer. The lesion has a great tendency to scar formation, which at times breaks down to form new ulcers and is resistant to all types of treatment. Inguinal adenopathy is generally present but is never an outstanding feature of the disease. Urinary symptoms occur only when the urethra is involved.

In several cases the condition has yielded to excision or curettage of the lesion associated with the usual hygienic regimen reserved for generalized tuberculosis. Radical amputation is reserved for cases in which the glans penis and urethra are hopelessly involved. The prognosis is good in primary tuberculosis of the penis that occurs in adults. When the lesion occurs in children after circumcision, the prognosis is extremely poor.

A complete summary of the literature dealing with primary tuberculosis of the penis occurring in adults is given. An interesting case is presented of primary tuberculosis of the penis occurring in a young adult following sexual exposure, which necessitated radical amputation of the penis.

BILHARZIASIS

Diamantis and Xylinas⁶⁵ described their experimental production of bilharziasis in guinea-pigs, from which they obtained the following results: In 12 control animals (5 guinea-pigs and 7 mice), all males, that received injections under the skin of the abdomen of an emulsion of cercarias, the disease did not develop, not even in 1 that was allowed to live for three months after the injection. Of the 8 guinea-pigs which

64. Lazarus, J. A., and Rosenthal, A. A.: Primary Tuberculosis of the Penis, *Tr. Western Branch Soc. Am. Urol. A.* **4**:70-86, 1935; *J. Urol.* **35**:361-377 (March) 1936.

65. Diamantis, A., and Xylinas, E.: A propos de la reproduction expérimentale de la bilharziose chez les cobayes, *J. d'urol.* **41**:142-147 (Feb.) 1936.

served as subjects, the 2 that were infected by immersion of the penis in the emulsion died of cachexia, but neither of them presented the worms in any part of the portal system. In 1 of them, however, in which the liver was particularly affected, a small calculus, composed of calcium phosphate, was found in the bladder, as well as bilious and transparent urine. There can be no doubt that these animals died of hepatic insufficiency caused by intensive infection with the parasites. The questions arise why the parasites were not found in the portal vein and whether their death occurred before that of the animal. The authors were convinced that the parasites died first and that necropsy performed earlier would have revealed them in the liver.

Of the 6 other animals, which can be considered as having been infected by the classic procedure, none presented intestinal bilharziasis; that is, none had the worms coupled in the small ramifications of the mesenteric veins or eliminated them in their stools. Hence it must be recognized that among the 20 animals employed (13 guinea-pigs and 7 mice), some of which received injections of the emulsion while the others had the penis immersed in the emulsion, not even once was true intestinal bilharziasis found (with eggs eliminated in the stools), and only 2 infections were produced that were exclusively hepatic. The authors had the impression that they had delayed too long before killing some of the animals, for in the hepatic form, which is the one that as a rule develops in experimental bilharziasis in small animals, the parasites are far from being found at their ease in the hepatic trunk, that is to say, they are remote from any visceral mucosa, the submucous venules of which permitted them to copulate in the hepatic trunk, to lay eggs and to eliminate these. The authors concluded, therefore, that the hepatic trunk, far from being the favorite site chosen by the worms for their copulating and breeding, is simply a poor makeshift, a place where the worm, for lack of a better site, tries to get a foothold, not finding any venous recess short of the portal vein in which to ensconce itself.

UROGRAPHY

Minder⁶⁶ gave a detailed study on excretion pyelography, based on his experience in a Budapest urologic clinic. Retrograde and excretion pyelography are compared for different groups of diseases, and the value of both methods is illustrated by concrete cases. Minder stated that the problem of excretion pyelography does not lie in the technic of its application or in the indication for its use but in the judging of the pictures obtained. Such judgment may be obtained only after long experience.

66. Minder, Julius: Ueber den diagnostischen und klinischen Wert der Ausscheidungs-pyelographie, *Ztschr. f. urol. Chir. u. Gynäk.* 42:312-363 (Aug.) 1936.

Braasch and Emmett⁶⁷ reported on a study of excretory urograms to determine their value as a test of renal function. The intensity of visualization of the medium in the urogram, together with its time of appearance, was used as a basis for comparison. In a series of 50 cases of various diseases of the urinary tract in which both excretory urography and differential tests with indigo carmine were used, the results obtained with the two methods were in close agreement in 39 cases (78 per cent). In 11 cases (22 per cent), the results of the two tests did not agree. Further study of a large series of excretory urograms was then made, the cases being grouped according to individual pathologic lesions of the urinary tract. The degree of visualization was compared with the results of other tests of renal function that had been done and with the pathologic changes observed at operation or necropsy. In hydronephrosis, pyelonephritis, polycystic disease and solitary cyst of the kidney the urograms seemed to indicate quite accurately the renal function present, provided certain rules as to their interpretation were followed. With regard to renal tuberculosis and calculous disease, the intensity of visualization in the urogram was often inaccurate in its estimation of renal function. Indigo carmine seemed to be a better index, but it also was inaccurate. However, the additional data furnished by the urogram as to the anatomic deformity present render it a valuable adjunct in the diagnosis of these conditions. In the field of malignant renal tumors, excretory urography will often suggest the amount of function remaining, but it is not reliable as an index to the extent of neoplastic involvement. With urinary obstruction such as is observed in hypertrophy of the prostate gland, excretory urography gives valuable information as to renal function. In this condition the picture of the anatomic deformity is exceedingly valuable, as dilatation of the upper part of the urinary tract is common and can be produced even in the presence of a normal urea content in the blood.

Emmett⁶⁸ warned against making a diagnosis of a completely functionless kidney on the basis of the excretory urogram alone. It is not uncommon, in the presence of stone in the ureter or renal pelvis, to fail to obtain visualization of the involved kidney, and yet on cystoscopic examination an almost normal concentration of indigo carmine may be excreted promptly by that kidney. Faulty technic in making the urogram may occasionally be the cause of failure of visualization. This in no way lessens the value of excretory urography, for in most cases the exact amount of function remaining to a kidney is not the paramount issue, and in those cases in which visualization is not obtained,

67. Braasch, W. F., and Emmett, J. L.: Excretory Urography as a Test of Renal Function, *J. Urol.* **35**:630-642 (June) 1936.

68. Emmett, J. L.: Pitfalls in Interpretation of Excretory Urograms, *Proc. Staff Meet., Mayo Clin.* **11**:411-413 (June 24) 1936.

other means are available to determine the viability of the kidney in question. The author presented the clinical record of a man 36 years of age, who complained of severe dysuria, with tenesmus, frequency of urination and hematuria. Cystoscopy was performed with the patient under general anesthesia. Both ureters were catheterized easily, and there was no evidence of obstruction. Both ureteral specimens revealed the presence of blood but no pus. Gram stains and stains for acid-fast bacilli were all negative. An excretory urogram made with both ureteral catheters in place revealed a normal renal pelvis, calices and ureter on the right side, but there was no visualization on the left side, even in the fifty minute roentgenogram. The ureteral catheters were left in place for about twelve hours and continued to drain hemorrhagic urine. Renal tuberculosis on the left side with a practically functionless kidney was suspected; however, a definite diagnosis was deferred. Conservative treatment was instituted, and one week later the symptoms were markedly improved. An excretory urogram made at this time revealed definite evidence of function of the left kidney. A retrograde pyelogram gave evidence of a normal renal pelvis, calices and ureter on the left side. Conservative treatment continued to result in improvement, and the symptoms were entirely relieved approximately five weeks after the institution of treatment. At this time an intravenous urogram revealed an entirely normal-appearing left kidney, pelvis and ureter. The exact diagnosis in this case remained somewhat in doubt, but the case serves to demonstrate the occasional evanescent nature of reduced ability of the kidney to excrete a urographic medium.

ANESTHESIA

Tovell and Thompson⁶⁹ stated that almost any type of instrumentation can be accomplished following the induction of anesthesia by means of the intravenous administration of pentothal sodium.⁴⁴ The 42 patients who were subjected to prostatic resection were for the most part those whose prostate glands were of moderate size and from whom it was necessary to resect 15 Gm. or less of tissue. Manipulation of a ureteral calculus can usually be completed easily within the duration of the anesthesia, as can also the various other minor operative procedures which have been previously mentioned.

Pentothal sodium is an anesthetic agent well suited in urologic practice for many cases in which a general anesthetic is required. It is best suited for adults when the examination or operative procedure is expected to be completed within thirty minutes. The safe maximal dose of the drug for intravenous administration is 15 grains (1 Gm.).

69. Tovell, R. M., and Thompson, G. J.: Pentothal Sodium Anesthesia in Urologic Practice, *J. Urol.* **36**:81-87 (July) 1936.

Coughing, gagging and other movements which interfere with the operator are seldom if ever encountered. Occasionally a patient will be encountered whose body will destroy the drug rapidly, or an operative procedure may be more time-consuming than expected. In these rather infrequent instances, following the injection of 15 grains of the drug supplementary inhalation anesthesia may be employed satisfactorily.

Pentothal sodium provides a safe and pleasant method of escape from those usually painful minor procedures which formerly necessitated the use of inhalation anesthesia or caudal or sacral block. Because of this fact, certain unpleasant sequelae of the latter methods can now be avoided.

Caporale⁷⁰ presented a method of anesthesia which is termed by Dogliotti as peridural segmentary anesthesia and which has been accurately studied in the Surgical School of Turin, Italy. This type of anesthesia has been used in more than 300 cases of renal and ureteral disease within the past four years, with excellent results. It is now used in approximately 95 per cent of the surgical cases of reno-ureteral disease at this school. The method consists of an injection into one of the last dorsal intervertebral spaces of about 30 cc. of a relatively more concentrated anesthetic solution than that in use for local anesthesia. This solution rapidly spreads around the dura mater, which easily separates itself from the vertebral canal; the solution spreads itself superiorly and inferiorly for a region of about from eight to ten vertebral segments. Thus it easily infiltrates itself in the intervertebral canals, along the spinal nerves, following the perineural lymphatics for a long distance out of the vertebral canal. The spinal nerves of the infiltrated region, because of the peridural anesthesia, are therefore surrounded by the solution which penetrates them and causes in about from fifteen to twenty minutes an intense and complete anesthesia of the respective region.

During the anesthesia there is no sign of dangerous hypotension or of interference with the fundamental functions of life. The anesthesia lasts about two hours, after which there is a slow return of sensibility. There is no postoperative nausea or vomiting, no postoperative cephalalgia, no signs of consequent disease on the part of the liver or kidneys or of metabolic changes. In the last series of 100 cases in which this anesthesia was used, successful results were obtained in an average of 92 per cent. In 6 cases it was necessary to use small quantities of ether or gas in order to terminate the operation. In 2 cases it was impossible to make an injection.

70. Caporale, Luigi: Peridural Segmentary Anesthesia in Renal Surgery, *J. Urol.* **35**:403-407 (March) 1936.

URINARY ANTISEPTICS

Helmholz and Osterberg⁷¹ mentioned that the work of Rosenheim in England has demonstrated that phenylglycolic (mandelic) acid, when administered orally, escapes metabolism or conjugation in the animal organism and is secreted in the urine in a concentration sufficient for bactericidal action, provided the p_H of the urine is lowered simultaneously. The authors studied experimentally and clinically the excretory rate of phenylglycolic acid following the oral ingestion by man and the intravenous injection into dogs of the sodium salt. Criteria were established for the concentration of the acid and the p_H of the urine necessary for bactericidal action on numerous strains of organisms which had been isolated from the urine of persons with infections of the urinary tract. Rosenheim's method was employed for studying the concentration of phenylglycolic acid in urine, and the quinhydrone-electrode technic was used in determining the p_H of the urine. It was demonstrated experimentally that sufficient phenylglycolic acid was excreted in the urine of the dog subjected to a continuous injection, during a period of seven hours, of 700 cc. of 1 per cent solution of sodium phenylglycolate to establish a bactericidal concentration of phenylglycolic acid provided the p_H of the urine was lowered to an optimal level for bactericidal activity. Such an injection gave evidence that any injury produced in the kidney by the injection of a solution of sodium phenylglycolate is only temporary. It was demonstrated that at a p_H of 5.0, a concentration of phenylglycolic acid of 0.25 per cent was bactericidal for most organisms. In a similar manner, at a p_H of 5.3 a concentration of 0.5 per cent, and at a p_H of 5.7 a concentration of 1 per cent phenylglycolic acid, was bactericidal. Just as in the case of beta-oxybutyric acid, so for phenylglycolic acid: The lower the p_H , the lower the concentration of acid necessary to secure bactericidal action. Clinical findings were reported in 1 case in which 3 Gm. of phenylglycolic acid, in the form of a 10 per cent solution of the sodium salt, was ingested four times during the day. Ammonium chloride was given, in addition, to lower the p_H of the urine. A concentration of phenylglycolic acid in the urine in excess of 1 per cent was obtained. Results of experimental work with various strains of organisms is reported in some detail. Certain members of the *Aerobacter* and *Pseudomonas* groups were found to be far more difficult to kill than the organisms of the colon bacillus group. The bactericidal effect of phenylglycolic acid on organisms of the coccic group has not been studied for a large series of organisms, but several strains of staphylococci have been tested in single experiments and have been found to correspond roughly in vulnerability to the organisms of the colon bacillus group.

71. Helmholz, H. F., and Osterberg, A. E.: The Rate of Excretion and Bactericidal Power of Mandelic Acid in the Urine, Proc. Staff Meet., Mayo Clin. 11:373-377 (June 10) 1936.

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EIGHT YEARS' EXPERIENCE WITH THE ADRENAL GLAND

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Look at life as a whole—study its manifestations
in order and disorder, in health and disease.—*Osler*.

INTRODUCTION

The most characteristic features of the medical profession, features which distinguish it from all the other walks in life, are its dedication to the service of mankind and its devotion to the spirit of research. Medicine is the only world-wide profession the members of which follow everywhere the same methods, actuated by the same ambitions and pursuing the same ends. Its strength lies in this universal doctrine, and although it may be tinged with national characteristics, in its wider aspects it is a force which knows no country, which transcends all national limitations and which acknowledges no distinction of race, color or creed and no sovereignty but that of the mind. Science has done much to alleviate the unhappy conditions in which so many persons live. All this has been achieved by research on man, the unit, and much remains to be done. The vast improvement in his status, politically, morally and socially, which has been the promethean gift of science during the past century, can be traced directly to the wider application of knowledge derived from the individual. But evolution advances by such slow and imperceptible steps that to those who are part of it the finger of time scarcely seems to move. Nevertheless, the medical profession continues to exercise such a monopoly in charity as to be able to dispense gargantuan gifts, for it is now possible that within a few weeks any great discovery is broadcast and is practiced everywhere. Even if the individual efforts of members of the profession are lilliputian, they travel on hopefully—it is better than to arrive, and their happiness is to labor. Sooner or later some one will arrive to construct a master picture from the multicolored pigments all have struggled to provide. The true student, therefore, must become a citizen of the world; he must have freedom of intercourse and access without restrictions, for ignorance of work done elsewhere is but so

much time wasted. The evil, however, which besets all such good intentions is the sapping of one's energies by the stress of routine work.

HISTORICAL DATA

Mythology, art and sculpture throughout the ages have been acquainted with and have portrayed curious anomalies of the characters of one sex appearing in the other, which have always given rise to much speculation. In ancient times persons with such characteristics were regarded as an offense against nature, or as unclean and possessed of devils: The Greeks cast them into the sea, and even in later Roman times they were ordained to be flung into the Tiber. In 1474 a cock was sentenced and burned at the stake in Basel for the heinous and unnatural crime of laying an egg! In 1803, when the King Henry VII Chapel, Westminster Abbey, was restored after the neglect which it had suffered since the Dissolution of the Monasteries, over one hundred figures were found to be intact. Among them was one of Saint Wilgefort, who to avoid an unwelcome marriage prayed that she might become ugly and grew the beard with which she is shown. Her father, the king of Portugal, was so enraged that he had her crucified. Apparently the same fate befell all the sexually abnormal up to 1730. This primitive instinct of antipathy toward the abnormal or diseased can still be observed today among animals. Their presence in a herd is not tolerated; they are actively expelled or openly attacked. Achard and Thiers drew attention to a picture by Rebiera of Madeline Ventura, who, bearded at the age of 52, is shown suckling an infant. In the National Museum at Munich there is a statue in wood of the bearded Saint Madeline. At the Royal College of Surgeons there is a small book in French describing persons with characters of both sexes, accompanied by artistic representations, dated 1773. It is from mythology that one learns of transformations, both fantastic and picturesque. Sir John Bland-Sutton in his "Story of a Surgeon" stated:

We learn from Ovid, the master of romance and vivid fancy, that Tiresias in his youth interfered with two engendering snakes, and was in consequence turned into a girl. Seven years later, he saw the same pair of snakes again copulating and separated them with a stick. He was again turned into a man, and became the most celebrated philosopher in Thebes.

From Greek mythology one learns the story of Hermaphroditus, son of Hermes and Aphrodite, who was worshipped as a divinity. He had inherited the beauty of both his parents, and thus excited the love of the nymph of the fountain of Salmacis. She tried in vain to win his affections, and one day, while he was bathing in the fountain, she embraced him, praying that she should ever be united to him. The gods granted her request, and the bodies of the youth and nymph became joined together, retaining, however, the characters of each sex.

The figures of Hermaphroditus, half man and half woman, are common in ancient art. This double sex is also attributed to Dionysus and Priapus, embodying in one being the two principles of generation and conception. Dionysus, the young and beautiful but effeminate god of wine, is described as having a manly form but one approaching the female in its softness and roundness. It is interesting to trace these changes in the attitude toward the abnormal—from veneration to persecution, so to the modern conception of toleration, for science has realized that it is only by a closer study of the abnormal that one may hope to obtain a knowledge and better understanding of those normal processes by which one lives and has one's being.

EVOLUTION OF SEX

Evolution is the great law controlling all living things; biology touches the problems of life at every point—the laws governing growth, development, actions and interactions of living things. The study of these has revealed many deep secrets of generation, and the sesame of evolution has given one fairy tales of science more enchanting than "The Arabian Nights." This has all come about by the observation of facts, by their classification and by the founding on them of general laws. The main harvests have been reaped, but the physicians of today, the gleaners and winnowers, remain to leaven the loaf.

In the highest sphere of development—the vertebrate kingdom—there are present in each sex rudiments of the accessory sexual parts of the opposite sex. There are, however, exceptions to this rule. The bodily characters and the generative cells of both sexes are combined in a few persons, and these are spoken of as true hermaphrodites. In others, the generative cells of one sex are combined with the secondary sex characters of both. Such persons, the so-called pseudohermaphrodites, are more common than the true hermaphrodites, and the anomaly is usually seen in the female. True hermaphroditism is rare in man but is more common in animals. In pigs, for example, the incidence has been estimated at 1 in every 80,000. Pseudohermaphroditism is more common in man, and in Warsaw the incidence was computed as 30 to every 800,000 of the population. Both types are more frequent in animals. Sex reversal is another feature fairly commonly observed; a hen will acquire the plumage of a cock, and instances have been reported in which a fowl has functioned as both a hen and a cock. On the other hand, a pheasant has been described with male plumage on one half of the body and female plumage on the other half. I have observed an analogous case of hemihypertrophy in a boy (aged 6½ years), on whom adrenalectomy was performed for carcinoma on the side of the hypertrophy. I have examined a dozen hens which assumed male plumage (including one duck), and in most of

these there has been a lesion (generally carcinoma) of the ovary. I have observed a cow which after failing to calve exhibited all the characters of a bull in behavior. Unfortunately, its owner was more materially than scientifically minded, and a valuable specimen was lost for research. My observations on human beings in this paper are confined to women who have acquired the secondary sex characters of the opposite sex.

SEXUAL REPRODUCTION

Science so far has been unable to explain what determines sex. Among mammals, with rare exceptions, sex once acquired is definite and unchangeable, but this stability of the sexes totters and steadily declines as one descends the evolutionary scale. In man the differentiation of the sexes has come to be regarded so much an accepted and universal feature of nature that it is necessary to discuss the questions of sexual reproduction so as to obtain some idea of the different forms in which it is manifested in nature. But in all these forms the basis of reproduction is a variant or modification of the fact that the reproductive cell, either by an inherent capacity or by the conjugation with a reproductive cell of the opposite sex, is capable of forming a new individual.

In animals and plants with separate sexes it is obvious that the two elements must always unite for each birth. In true hermaphrodites it is not obvious why they should unite; nevertheless, they either occasionally or habitually do so for the reproduction of their kind. All vertebrate animals, all insects and some other large groups of animals pair for each birth. Many hermaphroditic animals do not habitually pair. The vast majority of plants are hermaphroditic. In plant and aquatic hermaphrodites cross-fertilization can be explained by such agencies as winds and insects on the one hand and currents on the other. Apparently no land animal is capable of self-fertilization. It is a curious anomaly that in plants some species of the same family are hermaphroditic and others unisexual, yet the difference between them is very small. Hence it appears that with plants and animals intercrossing between distinct individuals is almost a universal law of nature. Hermaphroditism may occur in varying degrees in one organism. It may be demonstrable in early life (tadpole) and disappear in adult life as maleness or femaleness predominates, or it may be normal in the adult. Other animals are bisexual; they produce ova at one time and spermatozoa at another. Certain facts suggest that hermaphroditism is a primitive condition and that the unisexual condition is a secondary differentiation. Yet other facts, showing that cross-fertilization may be difficult, suggest that the bisexual condition may have arisen as a secondary adaptation.

Another, though less understood, variant in the modes of reproduction is that of parthenogenesis, in which ova produced by the female develop without being fertilized by the male. This obtains among rotifers and small crustaceans, in which in some instances the males have never been found or are absent for a season. Among bees the males may be absent for the summer or may be artificially segregated for years without affecting the rapid succession of sterile female generations and the production of drones in the beehive from eggs which have never been fertilized.

Reproduction in the elementary forms of life is by simple cell division. Thus the ameba splits to form two complete individuals. For all its simplicity, its analogy is seen in the highest forms of reproduction, the same division of the fertilized ovum into two cells, each of which may ultimately develop into separate individuals—the so-called uniovular twins. In the metazoa the same primitive form of asexual reproduction obtains. In sponges, groups or clumps of cells sequester off to form new individuals, and if a sponge is cut into pieces these may regenerate the whole. In the higher forms of life this attribute of regeneration remains the sole legacy of the reproductive cells. Volvox, on the borderline between the protozoa and the metazoa, presents several peculiar biologic phenomena. The adults are balls of cells. In such a ball reproductive units are sent adrift and divide to form new individuals. At other times some of the cells develop into ova and others into spermatozoa. The large cells are fertilized by the small. There may be volvox balls in which only ova are being made and others with only spermatozoa. Here is an organism illustrating the differentiation between somatic and reproductive cells and occurring in asexual, hermaphroditic and unisexual phases. The analogy between the higher and the lower forms of life can be pushed even further. In the protozoa, processes corresponding to fertilization are of general occurrence. Periodically, conjugation takes place in which two individuals unite temporarily or permanently. This is an incipient sexual process—the fertilization of an ovum by a spermatozoon.

SEX CHARACTERS

Only when one set of sex glands (ovary or testis) predominates is it possible to determine the sex of the individual. These are called the primary sex characters. Associated with this predominance is the development of the correlated sex organs, and sexual maturity is declared by the acquisition of secondary sex characters, which are liable to much variation. When the sex glands are completely absent or experimentally removed, as in castration, the secondary sex characters shift toward the neuter or intersex type and not to the opposite sex.

The alternation of maleness and femaleness in the same individual occurs both naturally and experimentally. Sir John Bland-Sutton gave a most vivid description of this sex reversal in the Mexican swordtail:

It is a pretty fish, almost transparent and about three inches long. In sword-tails the sexes are distinct. In the male the anal fin is represented as a pair of claspers, and the lower part of the tail is elongated, and in shape like a sword. The female has a tail of the usual shape among carp—she produces viviparously. It happens not infrequently that after producing fry two or three times, she changes her sex completely. The anal fin becomes claspers, and the lower part of the tail elongates into a sword, as in the male. Indeed the female becomes male, not only in the assumption of male livery, but sheds milt. The change is correlated with the acquisition of functional testes.

Similar changes of sex have been described in fowls.

Another curious biologic phenomenon is presented by the so-called freemartin, the female twins of cattle, which not uncommonly exhibit sex abnormalities. They are sterile and resemble castrated cattle and their internal genitalia are undeveloped. In twins of different sexes the female is usually abnormal. It has been found that there exist connecting blood vessels between the fetuses and a fusion of the chorions. It has been suggested that the female undergoes masculation under the influence of androgen entering the blood of the female. When no such fusion of blood vessels obtains, the female is normal.

SECONDARY SEX CHARACTERS

The variety and intensity of secondary sex characters has been one of the most conspicuous features in evolution. The male animal differs from the female primarily in his increased power of locomotion, his special prehensile organs, his greater size, strength endurance and pugnacity and his special weapons of offense and defense; among birds, the male differs from the female by his gorgeous plumage and decorative ornaments, his engaging antics and his enchanting song. The females are naturally endowed with organs of nourishment and protection for the young. Darwin attributed the greater decorativeness of the males to the sexual selection exerted by the females. The handsomest and most vigorous males succeed in their courtship better than their rivals and are more successful in begetting a large number of offspring.

The theory of sexual selection is dependent on the laws of inheritance and on the transmission and development of characters. The equal transmission of characters to both sexes is the commonest form of inheritance. But characters are commonly transferred to that sex in which they first appear. Secondary sex characters are transmitted by both sexes, though developed in one. Occasionally characters proper to

the male appear in the female, when she grows old or becomes diseased, for example, in the common hen. The first development of characters in the female and transference to the male is less commonly observed. Reversion of characters, which may have been transmitted through two or three generations or many generations, may appear under certain unknown favorable circumstances.

It is not known why certain characters should be inherited by both sexes and other characters by one sex alone, namely, by that sex in which the character first appeared; but it seems in a general way that variations which originate late in life tend to be developed in the same sex alone while variations which first appear early in life in either sex tend to develop in both sexes. In a few cases it must be assumed that there is an embryonic difference in the sexes to account for some characters which are seen only in one sex. For instance, hemophilia is transmitted from the parent male through the daughters, who remain unaffected, to their sons. The same obtains in some forms of color blindness. It is probable that the parent transmits characters of the asexual type which are capable of reacting to the male and the female influence of a given species.

Hair, which may be considered a secondary sex character, holds an anomalous position. It seems probable that man is descended from some hairy progenitor, yet the loss of hair must have been an inconvenience to primitive man. The commencement of denudation is seen on the under-surface of the female anthropoid ape. As women are less hairy than men, females apparently first had their bodies denuded of hair, possibly as a sexual attraction, and transmitted this character equally to both sexes. On the other hand, the male apelike progenitors of man acquired beards as a sexual ornament and transmitted them to their male offspring.¹

HISTORY OF THE ADRENOGENITAL SYNDROME

As long ago as 1756, W. Cook established the association of hypertrichosis and adiposity with tumor of the adrenal gland. The association of secondary sex changes with tumor of the adrenal gland was known to John Hunter, and though cases were sporadically recorded, they were unsatisfactory owing to a lack of detailed pathologic investigation. It was not until 1905 that the subject was brought into prominence, in a publication by Bullock and Sequeira² in which eleven cases were

1. Broster, L. R.: A Review of Sex Characters, with Special Reference to the Adrenal Cortex, *Brit. M. J.* **1**:743-748 (May 2) 1931.

2. Bullock, W., and Sequeira, J. A.: On the Relation of the Suprarenal Capsules to the Sexual Organs, *Tr. Path. Soc. London* **56**:189, 1905.

reported, all in children under the age of 15 years. There were also records of cases of tumor, both benign and malignant, in a few of which the growth had been removed surgically, but the association of tumor with cortical hyperplasia was confined to postmortem observations. But apart from such generalizations, there was no indication as to how the adrenal cortex or its precise pathologic structure was implicated as a causal factor. All physicians are familiar with the varieties of tumor of the adrenal gland; the tumors are spoken of generally as hypernephromas and are similar in origin, outward appearance and microscopic texture. But why only a minority are associated with virilism while the majority are not remained an enigma. This was briefly the state of knowledge when the present investigations were started.

HISTORY OF PRESENT RESEARCH

In 1927 I was asked by my colleague Dr. Gordon Holmes to remove an adrenal gland from one of his patients, a young girl with virilism, from New Zealand. By 1930, with the cooperation of Dr. Harold Gardiner-Hill, we were able to publish in the *British Journal of Surgery*³ a paper in which our clinical material was sifted and classified into satisfactory groups. We were assisted in the histologic observations by Dr. J. G. Greenfield. By 1933 my colleague Dr. H. W. C. Vines was able to undertake a more detailed study of my pathologic material, and published a short monograph,⁴ which presented a decided advance in knowledge in that Dr. Vines had been successful in finding a differential stain (the ponceau fuchsin stain) which when applied to the adrenal gland of any patient with virilism who was subjected to unilateral adrenalectomy gave a positive reaction but when used on the adrenal gland of a normal control gave a negative reaction.

THE ADRENOGENITAL SYNDROME

The adrenogenital syndrome may be defined as that condition in which secondary male sex characters appear in the female. It is associated with a retrogression of the primary and secondary feminine sex characters and their functions. The clinical picture is determined by the type of lesion and the age of the patient. Hyperplasia, owing to its slow growth, is not likely to produce such rapid changes in the

3. Broster, L. R.; Gardiner-Hill, H., and Greenfield, J. G.: The Adrenogenital Syndrome Associated with Cortical Hyperplasia: The Results of Unilateral Adrenalectomy, *Brit. J. Surg.* **19**:557-570 (April) 1932.

4. Broster, L. R., and Vines, H. W. C.: The Adrenal Cortex: A Surgical and Pathological Study, London, H. K. Lewis & Co., Ltd., 1933. Broster, L. R.: The Adreno-Genital Syndrome, *Lancet* **1**:830 (April 21) 1934.

sexual sphere as a malignant tumor, which is usually rapidly fatal, while the course of a benign adenoma is intermediate between the two. The age of the person when the adrenal condition develops also plays an important part. As can be readily understood, the effects of the lesion will vary according to whether the organism is immature or fully developed at the time of onset.

Symptomatology.—The features of the adrenogenital syndrome are presented in the following outline:

1. The appearance in the female of hair according to the male pattern and distribution.



Fig. 1 (case 2).—Photograph of a patient with adrenal pseudohermaphroditism, showing a muscular masculine build, absence of breasts and a male distribution of pubic hair.

2. Alterations in bodily contour toward the male sphere:

- (a) Overgrowth of skeletal structures such as muscle and bone, lessening of the subcutaneous fat and coarsening in the texture of the skin.
- (b) Broadening of the shoulders relative to the pelvic girdle.
- (c) Enlargement of the clitoris.
- (d) Deepening of the voice.

3. Immature development of the female genitalia, both external and internal, and degeneration of the ovaries, giving rise to amenorrhea, either primary or secondary, or to disturbances of menstruation. There may be absence or underdevelopment of the breasts.

4. Psychologic abnormalities.

Hypertrichosis.—Male hair in the female varies in texture and distribution. It ranges from the curly crisp variety to the soft downy type, which is patchy. On the face it may take the form of a beard and mustache or that of "mutton chop" whiskers. On the trunk the hairs extend triangularly to the umbilicus from the pubis; they may cover the midsternal or lumbosacral region and the shoulders or form a halo round the nipples. The perineum and axillae are more densely covered. On the limbs they grow thickest over the thighs or on the legs and forearms, and the male mimicry may be complete to tufts of hair on the dorsa of the feet or on the proximal phalanges. In older women apical baldness and temporal recession may be conspicuous.

Changes in Bodily Contour.—The bodily contour varies with the time of onset and the degree of virilism. Persons in whom virilism



Fig. 2 (case 2).—Photograph of the same patient pictured in figure 1, showing a beard and mustache.

develops early are more masculine in appearance than an underdeveloped boy. They are short, thick set, broad shouldered, deep chested and narrow hipped, and the muscles of their limbs stand out prominently under a layer of coarse skin with little subcutaneous fat. When feminine growth has been established, no such marked alteration can take place, but there is usually some indication of variation, such as a lessened disproportion between the relative breadths of the pectoral and pelvic girdles, a tendency to "heftiness" and an undue hint of prominence of the superciliary ridge or the jaw, which is especially noted roentgenographically.

The breasts tend to be underdeveloped. There may be complete absence of both breasts; some never develop fully and others mature and then retrogress; when large, they are composed of much fatty tissue. Microscopic section of some breast tissue removed for an adenoma

in a case of virilism showed those involutionary changes which occur later in life.

In a few cases there has been some enlargement of the larynx, but in a larger porportion the pitch of the voice is altered, being deeper in tone and rough or husky. This may not be apparent in normal speech, but in moments of excitement or animation its true quality is revealed.

Changes in the Female Genitalia.—The main changes are enlargement of the male elements, with diminution of the feminine ones. The clitoris is invariably enlarged and may possess a definite glans and prepuce. When this is marked, its under-surface is grooved, as in hypospadias, but the urethra is in its normal position at the top of a small and undeveloped vagina. The mons veneris and the labia are small

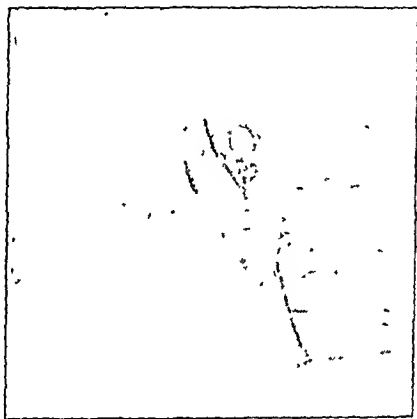


Fig. 3 (case 2).—The external genitalia, with an enlarged clitoris with a glans, of the patient shown in figure 1.

and undeveloped. Laparotomy has revealed constant changes in the ovaries and a diminution in the size of the fundus of the uterus and cervix. The ovaries have been degenerate. They have been enlarged up to the size of a golf ball and pale, fibrotic and studded with small cysts, or, more rarely, they have been small and fibrotic and even calcareous. The fundus of the uterus has been as small as a thumb-nail and the cervix diminutive.

Amenorrhea may be primary—i. e., the menses never appear—or, more commonly, secondary. In the latter case menstruation starts normally and proceeds regularly, but usually either at the time of or soon after the appearance of hirsutism it becomes irregular, the intervals lengthen and the flow becomes shorter in duration, with less loss, until it finally ceases, or there may be long intervals of amenorrhea.

Changes in Psychologic Outlook.—There is a fairly high percentage of nervous and mental illness among these patients, and a great deal of it can be traced in their family histories. Briefly, they are normally heterosexual, homosexual or narcissistic, or they may present a combination of any of these three manifestations. They are pitifully conscious of their disabilities and in their silent suffering reveal the saddest aspect of human emotions.

CLASSIFICATION OF THE ADRENOGENITAL SYNDROME

The following classification was suggested from our series of cases in which unilateral adrenalectomy was performed:³

1. Adrenal pseudohermaphroditism.
2. Adrenal virilism.
3. Achard-Thiers syndrome, probably allied to Cushing's syndrome.



Fig. 4 (case 2).—The largest adrenal gland removed in this series of cases. The gland gave a strong fuchsinophilic reaction.

4. Postmenopausal virilism—the latest variety, associated with hypertrichosis, apical baldness, enlargement of the clitoris and a tendency toward obesity.

GROUP 1.—*Adrenal Pseudohermaphroditism.*—This is the most complete form of the syndrome. The changes occur before the bodily form and sex organs have become differentiated, and there are marked virilism, hypertrichosis of the male type, primary amenorrhea and an absence of normal feminine development.

GROUP 2.—*Adrenal Virilism.*—A later variety, in which the adrenal changes set in after puberty, is associated with alterations in the bodily form and in the external sex organs, hypertrichosis of the male type and a disturbance of sex functions. Owing to the later development of the lesion of the adrenal gland, the normal bodily changes of puberty and a period of normal menstruation are followed by regressive changes in both spheres, bodily changes toward masculinity, a diminution in

the size of the breasts and a diminution in the menstrual flow. There are in this group a relatively large number of cases, if those in which mild hypertrichosis with or without slight changes in the menstrual rhythm are included. Some of them might be described as instances of familial hirsutism. My co-workers and I have investigated other cases but have not considered the clinical condition severe enough to warrant adrenalectomy, or we have found on laparotomy no marked disproportion in the size of the adrenal glands, so that we could not expect any marked improvement by the removal of one.

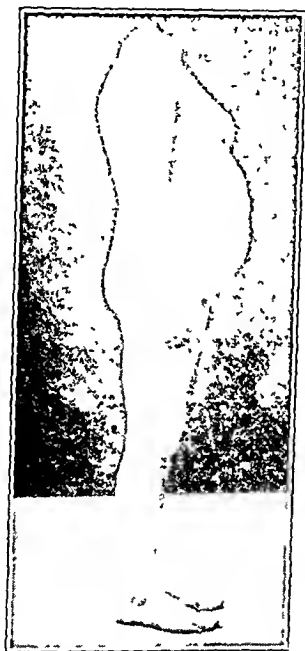


Fig. 5 (case 3).—Photograph of a patient with Cushing's syndrome.

GROUP 3.—*The Achard-Thiers Syndrome*.—In this group the lesion of the adrenal gland appears to be one element in a multiglandular syndrome. The patient presents the symptom complex described by Achard and Thiers⁵ as “diabetes of bearded women,” a condition found at autopsy to consist of hyperplasia of the adrenal gland associated with changes in the other ductless glands. The chief symptoms are hypertrichosis on the face of the male type, obesity, glycosuria with a decrease in the tolerance to carbohydrates, hypertension and usually amenorrhea, but without other signs of virilism.

5. Achard, C., and Thiers, J.: La virilisme pileire et son association à l'insuffisance glycolitique (diabète des femmes à barbe), Bull. Acad. de méd., Paris 86:51, 1921.

The onset of the main symptoms in these groups may be summarized as follows:

Average age of patients	20 years
Average age of onset of menstruation.....	14 years
Average age of onset of virilism.....	15 years
Average age of increase of weight.....	16 years
Average age of menstrual irregularity	18-20 years

Here the onset of virilism is followed by a period of endocrine imbalance, as shown by the increase in weight. In group 2 this is temporary, whereas in group 3 it becomes permanent. The conditions of group 3 are difficult to determine. We have investigated several cases, performed laparotomy in a few and removed the adrenal gland in a case considered now to be one of Cushing's syndrome in which uni-



Fig. 6 (case 6).—The smallest adrenal gland removed in the series of cases. The gland gave the most marked fuchsinophilic reaction of all of those removed.

lateral adrenalectomy was not followed by much change, although the tissue gave a positive reaction to the ponceau fuchsin stain. The patients are all fat, hairy women with irregular menstruation. The manifestations vary in detail, but all the patients tend to show glycosuria, a high sugar curve, hypertension, erythrocythemia, a high color index and hypercholesteremia. The condition may begin as adrenal virilism and later exhibit many of the symptoms of Cushing's syndrome.

PREOPERATIVE INVESTIGATIONS

Laboratory investigations have given mainly negative results, but with rare material of this kind it is essential that every case should be fully investigated. In this series the calcium, phosphorus, cholesterol, urea and sugar contents of the blood, the gastric acidity, the sugar tolerance curve and the effect of insulin on the fasting patient have been investigated. The last-mentioned experiment was designed to see what

resistance these patients had to insulin. They were all within normal limits. The sugar tolerance curves in the majority of cases showed some distortion from the strictly normal response in that there was a normal elevation from the fasting stage but a slower return to normal. The insulin test was generally unsatisfactory from the point of view of drawing any conclusions, but there was a tendency for the patients to show a resistance to insulin. A routine roentgenogram of the sella turcica should be made. The pituitary fossa is invariably small. A roentgenogram should also be made after the injection of iopax. In this way it may be possible to detect a tumor of the adrenal gland,



Fig. 7 (case 5).—Photograph of a patient with adrenal virilism, showing a masculine muscular build, small breasts and a male distribution of hair on the abdomen, chest and shoulders.

either by distortion or by relative displacement of the renal pelvis on one side. In spite of this information, the only reliable method is direct palpation by means of exploratory laparotomy. The relative sizes of the adrenal glands can be estimated, a search can be made for accessory adrenal glands and any changes in the uterus and ovaries can be detected.

SURGICAL APPROACH

The transthoracic route has been used for operation in the majority of cases, gas and oxygen anesthesia being employed. This is the easiest approach, in view of the fact that the vascular pedicle of the adrenal

gland allows a slight range of upward movement and that the excursions of the diaphragm are better controlled by incision and retraction. It has the disadvantage of creating an artificial pneumothorax, with its concomitant respiratory distress and a long period of incumbency until the lung expands. Artificial pneumothorax has been induced prior to operation, but as it does not obviate the main issue it cannot be said that it affords any greater advantages. To overcome these difficulties a subdiaphragmatic route has now been attempted, by fracturing the last rib at its neck and retracting this upward with the diaphragm. This exposure is more difficult, and the delivery of an adrenal gland



Fig. 8 (case 5).—Back view of the same patient shown in figure 7. The hair is especially thick between the shoulders, on the small of the back and on the limbs.

may be impeded by sudden diaphragmatic movements, which can be controlled only by expert anesthesia under increased pressure. On the whole, it is a decided improvement, and in our later cases the patient has been discharged within a fortnight of the operation. Inaccessibility, deep bleeding and delicate traction on a friable organ through a confined space which may spasmodically contract are the main difficulties.

OPERATIVE RESULTS

The patients submitted to unilateral adrenalectomy have shown no untoward sign so far as their general physical condition and well-being

are concerned. It is perhaps too early to speak of the ultimate value of the operation, and no hard and fast rules can as yet be laid down with regard to the selection of patients. As a generalization, it may be said that there has been a definite tendency toward the restoration of the menstrual function, and in cases in which the condition is obstinate the injection of estrogen has been useful. Another striking effect within twenty-four hours after operation is that bunches of acquired hair can be pulled out with little or no pain. These hairs grow again but gradually lose their virile character and tend to become thin, attenuated and sparser. In a few cases there has been a slight change in color.

That any dramatic change can take place is not to be expected. So far, only that adrenal gland has been removed which on palpation at



Fig. 9 (case 4).—Photograph of a patient with adrenal virilism, showing "mutton-chop whiskers." The patient gave birth to a son after adrenalectomy.

laparotomy has been considered to be the larger, though both are involved. That both adrenals are involved has been pointed out by Lescher and Robb-Smith and by Geoffrey Bourne. The left adrenal gland has been removed more often than the right. It must be recalled that the other adrenal gland may hypertrophy in the same way that surgical removal or disease of one kidney causes hypertrophy of the other or removal of half the thyroid may be followed by an enlargement of the other lobe. The largest adrenal gland measured 7.5 by 7.5 cm., and one of the smallest was 4 by 2.1 by 1.5 cm., with a weight of 3.3 Gm. (normal weight, 4.7 Gm.). The latter gland was within the limits of normal, but it gave the most intensely positive fuchsinophilic reaction. These findings suggest that virilism does not necessarily

depend on hypertrophy alone but may be associated with an apparently normal adrenal gland.

Encouraging results have been obtained only in cases of postpubertal virilism (group 2). In cases of prepubertal virilism (group 1) they



Fig. 10 (case 13).—Flat-chested, slender type of patient with adrenal virilism.

have been disappointing, but this is to be expected, for an operation performed during the second decade is too late for a condition which manifests itself only at puberty and has been present for a considerable time. At present there is no method of determining adrenal dysfunction before puberty. If this were possible, the results of earlier operations would be equally good. Time must of necessity be the final judge of

a speculative surgical procedure. A condition of slow or late development can be expected to retrogress slowly when only part of its cause has been removed.

PSYCHOLOGIC RESULTS

It must not be supposed that every woman with virilism has psychologic changes or abnormalities. When the sexuality is normal, it is normal after operation. On the other hand, we have seen abnormal



Fig. 11 (case 11).—Masculine type of patient with adrenal virilism, showing marked hirsutism.

sexuality return to normal after operation, such as changes from homosexuality to normal heterosexuality. Briefly, it may be said that operation can effect changes in personality.

"It is an error of our day that in the treatment of the human body physicians separate the soul from the body." Since these words were uttered by Socrates, physicians have separated into different sciences, but his sentiments remain the same, for it cannot be said that there has been any real rapprochement between the psychologist and the

clinician. That they have never been able to meet on common ground is perhaps understandable, because psychology is not an exact science in the same sense as the other natural sciences. The psychology of sex looms large in the teachings and writings of the psychologists, but it has received scant attention from the clinician. The latter knows little of the complex chemical interactions taking place within the cells and tissues of the human body, but with increasing knowledge dare one not hope that some of the simple and basic problems of normal and perverted sex psychology may be explained in part by organic means? Our observations in this work have encouraged us in this hope, and future research may profit greatly by a cordial cooperation between these sciences.



Fig. 12 (case 19) —Photograph of a patient with adrenal virilism with a masculine type of face

DIFFERENTIAL DIAGNOSIS

In dealing with the question of differential diagnosis, I feel obliged, at the expense of confusing the issue, to report several recent cases in which the pathologic diagnosis has been proved. This is done in order to stress the clinical and pathologic aspects. By this means one may gain a wider outlook, by being able to visualize the controlling mechanism and the developmental processes involved in the production of sex characters.

Arrhenoblastoma.—The first case is one of clinical virilism associated with an arrhenoblastoma of the ovary (verified by Professor Schockaert, of Louvain⁶).

6. Schockaert, J. A. *L'arrhénoblastome. Notes cliniques et physiopathologiques*, Louvain, Imprimerie, Nova et Vetera, 1936

A woman aged 26, who was contemplating marriage, complained that her periods became irregular at the age of 19 and ceased at 21. At the same time hair began to grow according to the male distribution. The breasts began to recede, the subcutaneous fat began to disappear, the voice changed and the patient became morose and no longer felt attracted by men. After removal of an ovarian tumor, she began to lose her hair, her periods recommenced, her depression ceased and she began to feel like a normal woman again. Dr. Vines examined a section of the tumor but could not obtain a positive reaction to the fuchsin stain. However, if one considers the ovary to be essentially a bisexual organ, in which the medulla is of testicular origin,⁷ it is not difficult to envisage such a change in sex characters which are normally under control of the gonad. There is no definite proof of this view. On the other hand, an arrhenoblastoma may be regarded as a definite testicular implant in the ovary (Vines).



Fig. 13 (case 20).—Photograph of a patient with adrenal virilism with a marked beard.

Tumor of the Hypothalamus.—The most recent case (which I was privileged to see clinically) in a series of five verified cases of virilism in the male due to hypothalamic tumor was described by Le Marquand and Russell.⁸

The patient died of rheumatic fever at the age of 5 years. At the age of 3 months he suffered from vomiting; at 14 months pubic hair began to grow, and

7. Woollard, H. H., and others: Discussion on Suprarenal and Pituitary Tumor and Their Correlation with Experimental Findings, *Proc. Roy. Soc. Med.* 27:271-282 (Jan.) 1934.

8. Le Marquand, H. S., and Russell, Dorothy S.: A Case of Pubertas Praecox (Macrogenitosomia Praecox) in a Boy Associated with a Tumour in the Floor of the Third Ventricle, *Roy. Berkshire Hosp. Rep.*, 1934-1935, pp. 31-62.

this was followed by abnormal development of his sexual organs and rapid bodily growth. His mental development corresponded with his age, but psychologically, although normally heterosexual, he was precocious in that he made obvious sexual advances to adult women. At autopsy a small tumor was found attached to the right corpus mamillare and the tuber cinereum. The adrenal gland gave a negative reaction to the fuchsin stain.

Dott and Cappell⁹ observed the first well defined case of pubertas praecox associated with a hypothalamic lesion in the female

A girl, who died at the age of $8\frac{1}{2}$ years from scarlet fever, suffered from fits soon after birth. At the age of 6 months she began to menstruate; at 9 months her breasts enlarged, and at 12 months hair developed. The child increased rapidly in stature for four and a half years. Mentally she showed a precocity for remembering tunes, and psychologically she was homosexual, preferring the



Fig. 14 (case 21) —Photograph of a patient with adrenal virilism with a goatee variety of beard.

company of adult women. From the age of $4\frac{1}{2}$ onward, she showed a definite physical and mental progeria. At autopsy, Professor Cappell, of Dundee, verified and localized a benign astrocytoma arising from the neighborhood of the mamillary bodies and involving the posterior half of the floor of the third ventricle. The tuber cinereum was pushed slightly forward but was not actually involved. The tumor bulged into the third ventricle and filled the interpeduncular space.

The condition in this case is therefore the direct counterpart of that occurring in males and is most interesting in view of the fact that the only other tumor in this region which causes sex precocity—a tumor of the pineal body—has been recorded only in boys.

Cushing's Syndrome.—The association of Cushing's syndrome with a basophil adenoma of the pituitary gland is so well known that it

9. Dott, N. McO., and Cappell, D. F.: Personal communication to the author.

facilitates any discussion on the subject. I have already drawn attention on clinical grounds to a large group of cases in which many of the primary and intermediate symptoms of this syndrome are presented, and with a multiglandular condition of this sort it is to be expected that there would be a similar variation in the pathologic process. To prove that this is so, I wish to draw attention to the following facts which have come to my attention.

(a) Two cases of the Cushing type associated with carcinoma of the adrenal gland and a cyst of the pituitary body.

1. A woman aged 33 had increasing hirsutism, obesity and amenorrhea, frequent headaches, vomiting and baldness. A carcinoma of the

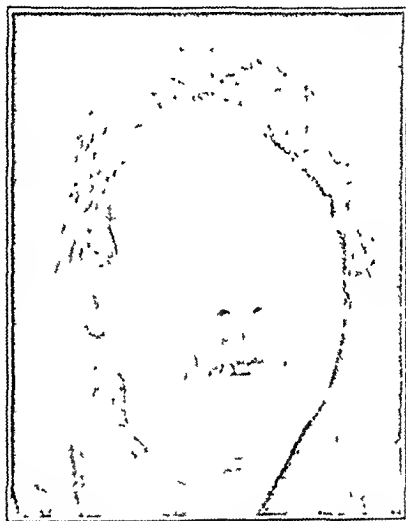


Fig. 15 (case 22).—Photograph of a patient with adrenal virilism with a mustache.

adrenal gland was found, the gland being four times the normal size. It gave a weakly positive reaction to the fuchsin stain. A cyst was found in the pituitary body.¹⁰

2. A woman aged 51, who was married at 39, after the birth of the youngest child had amenorrhea, hirsutism, baldness, deepening of the voice, an increase in weight, headache and failing vision. The blood pressure was 186 systolic and 116 diastolic. An adenocarcinoma of the right adrenal gland was found, with a secondary metastasis in the lung and a cyst in the pituitary body.¹¹

10. Hare, D. C.: Two Cases of Dyspituitarism, *Proc. Roy. Soc. Med* **27**: 1017-1020 (June) 1934.

11. Unpublished data. Personal communication between H. W. C. Vines and Professor Webb.

(b) In two cases virilism clinically indistinguishable from Cushing's syndrome was found to be due to tumor of the adrenal gland (Lescher and Robb-Smith¹² and Hare, Ross and Crooke¹³). In one of these the fuchsin stain elicited a positive reaction not only in the tumor but in the opposite adrenal gland. In one case there was a slight increase in the basophil cells of the pituitary body.

(c) Data on five cases of proved basophilism of the pituitary gland have been collected at the Charing Cross Hospital. In each of the cases the adrenal glands gave a negative reaction to the ponceau fuchsin stain, and in no case were there any of the clinical signs associated with virilism or with Cushing's syndrome. In a sixth case of mild virilism associated

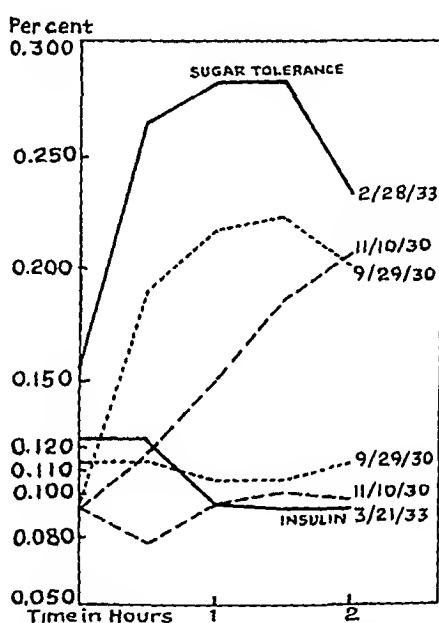


Fig. 16 (case 3).—Sugar tolerance curves made after removal of the right adrenal gland and one curve made after the administration of insulin.

with narcissism the patient died of a pulmonary embolus after appendectomy, and we found a well marked nodular basophilism of the pituitary gland. The adrenal glands gave a negative reaction to the ponceau fuchsin stain.

(d) One case is of particular interest in that Vines discovered a small meningioma, the size of a pea, situated at the attachment of the

12. Lescher, F. Graham, and Robb-Smith, A. H. T.: A Comparison of the Pituitary Basophilic Syndrome and the Adrenal Cortico-Genital Syndrome, *Quart. J. Med.* 4:23-35 (Jan.) 1935.

13. Hare, D. C.; Ross, J. M., and Crooke, A. C.: Cortical Carcinoma of the Suprarenal with Cushing's Basophil Pituitary Syndrome, *Lancet* 2:118-122 (July 20) 1935.

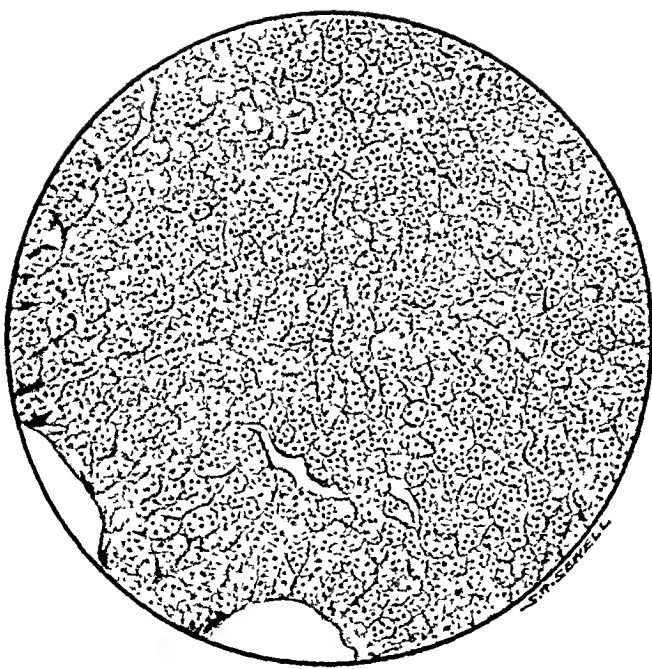


Fig. 17.—Photomicrograph of the adrenal cortex in a case of virilism. The fuchsinophilic reaction was positive.

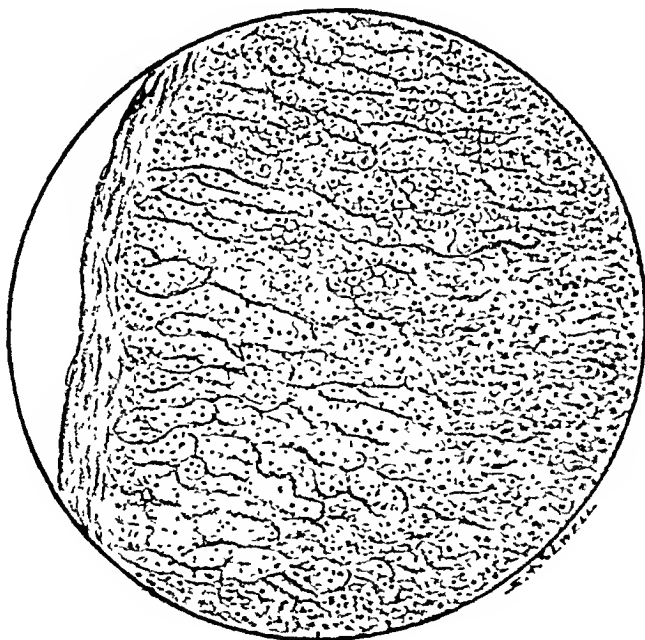


Fig. 18.—Photomicrograph of a normal adrenal gland removed at nephrectomy. The fuchsinophilic reaction was negative.

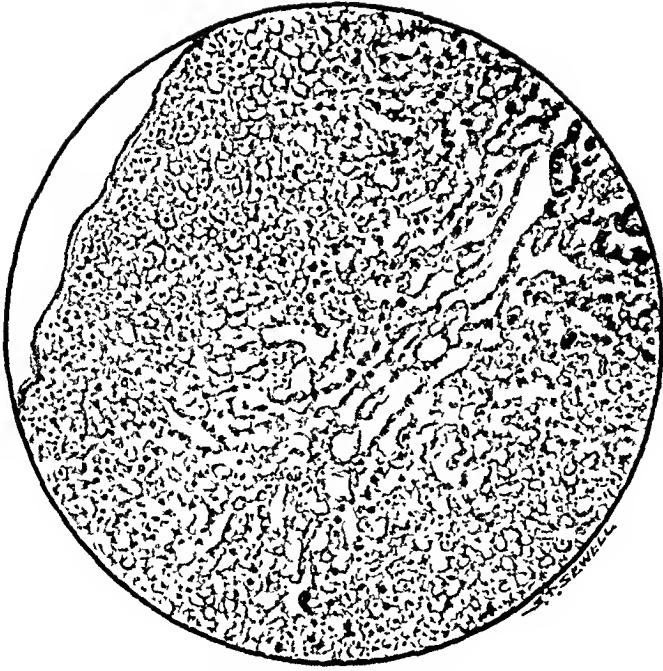


Fig. 19.—Photomicrograph of the adrenal cortex of a 16 week male fetus.
The fuchsinophilic reaction was positive.

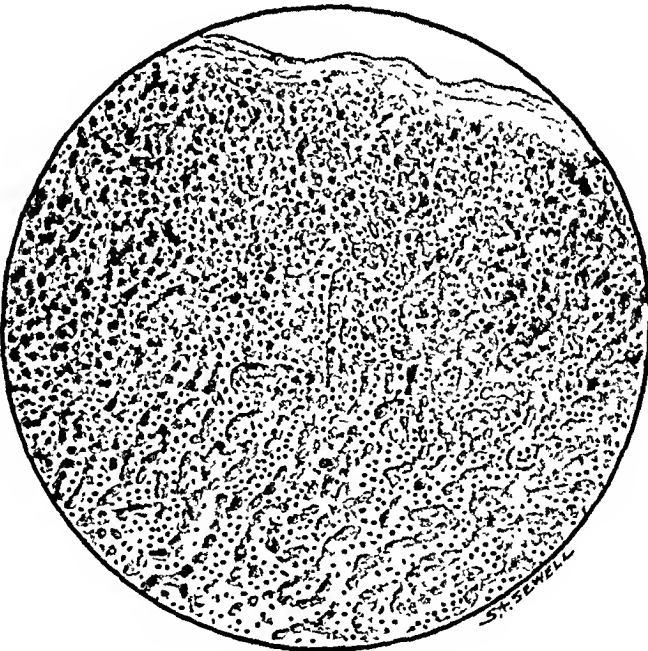


Fig. 20.—Photomicrograph of the adrenal cortex of a 15 week female fetus.
The fuchsinophilic reaction was negative.

stalk of the pituitary body to the hypothalamus. The patient was a slim young woman of 23, who died of chronic nephritis. She had a masculine body with fairly marked hypertrichosis; the adrenal glands were normal and the ovaries were cystic. There was no obvious evidence of an endocrine disturbance, and the only effects were those of hypothalamic pressure.

APPLIED HISTOLOGY (PONCEAU FUCHSIN STAIN)

With this range of clinical material it was possible to argue that if no irregularity was found in the arrangement or shape of the cortical cells there might possibly be a difference in their function. By using the ponceau fuchsin stain, Dr. Vines was able to show that in our series of cases of virilism in which unilateral adrenalectomy was performed the cytoplasm of the cells of the cortex contained a vivid red granular material, mainly in the inner and the middle zone. The color varied in intensity and was most vivid in an adrenal gland which was within the normal limits of size, suggesting that the response was as much qualitative as it was quantitative in the case of hyperplasia.

To exclude the possibility of postmortem changes taking place in the adrenal gland, a control series was started by removing portions of normal gland in the course of routine operations on the kidneys. These all gave negative reactions to the stain, as did all normal adrenal glands studied post mortem. A collection of several autopsy specimens of tumor of the adrenal gland associated with virilism gave a positive reaction, showing that the fuchsinophilic material in the cells is capable of surviving postmortem conditions. It seemed unlikely that some isolated reaction had been obtained in the adult; so a further search was made into fetal adrenal glands. Dr. Vines found a strong fuchsinophilic reaction in the male fetus between the ninth and the seventeenth week. In the female fetus the reaction was not so strong and of shorter duration, lasting from the eleventh to the fourteenth week. After the twentieth week it was absent in both sexes. This observation may well prove to be one of fundamental importance in the elucidation of many difficulties. It establishes an early and passing phase in embryology, common to both sexes, but less marked and of shorter duration in the female.

In other tissues of the body traces of this reaction were found in the interstitial cells of the testis, the corpus luteum and the anterior lobe of the pituitary gland.

Our clinical evidence and operative results have established this differential staining reaction with the condition of maleness in the female, and this has naturally suggested the possibility that "the substance so staining must be closely related to or even identical with the

male hormone or its precursor"¹⁴ and that its presence in the inter-cellular spaces further suggested that it acted by way of the blood stream. We have already drawn attention to the tendency toward hypercholesteremia, and the adrenal gland has long been credited with the regulation of the sterol metabolism. Furthermore, the presence of this stain is associated with a benign growth of tissue in bone, muscle, fat and skin alien to its normal host. Doubt has been cast by Bourne¹⁵ on our interpretation of the fuchsin stain, and he expressed the opinion that it may be due to mitochondrial changes occurring in the cortical cells. In an ingenious theory he links up this subject with the work of Dodds, who showed that the androgenic and estrogenic substances are derivatives of the sterols and are chemically linked to the coal tar substances of carcinogenic activity. He also stated that carcinogenic principles may be discovered in the interaction between the cortical cells and the sterol metabolism.

COMPARATIVE ANATOMY OF THE ADRENAL GLAND

In order to obtain a clear conception of the background of our work, it is necessary to refer briefly to the comparative anatomy of the adrenal gland and to trace the steps which have led to the formation of this highly specialized organ.

In its primitive form the cortex is separate and intimately connected with the reproductive system. It then becomes associated with the cells of quite a different system, the sympathetic, which ultimately forms the medulla. It appears first in fish and increases in importance so that the glands become essential to life in the high animals. In sharks and rays the two cell systems are separate. The cortex is known as the interrenal body and is associated with a marked development of the sexual system. In amphibians (frogs) the two cell systems make a definite advance toward each other and are arranged in a chain along the lumbar segments, until in reptiles and birds one finds them intimately mixed to form a solid organ. In mammals and man the medulla becomes completely enclosed within the cortex, and the method by which these sympathetic cells wander into the cortex in man has not been observed even in the higher apes. From the nature of such a migratory process it is not uncommon for cells to become detached and to form accessory adrenal glands, which may contain the elements of one or the other or of both of these cell systems. In man the adrenal glands reach the maximum size of their development at birth, when each is about one-third the size of the kidney. The inner layers of the cortex

14. Adrenal Virilism, editorial, *Brit. M. J.* 2:880 (Nov. 11) 1933.

15. Bourne, Geoffrey: The Sterols, Sex Hormones, and Cancer, *J. Cancer Research Com. Univ. Sydney* 7:34-39 (Aug.) 1935.

then undergo an astonishing and rapid process of absorption and regeneration, until the size of the gland is reduced to one thirtieth of that of the kidney. The glands enlarge at puberty, during pregnancy and at the menses. Between the fourth and the fifth decade they reach their zenith, and then they gradually undergo senile involution. It occasionally happens that this adult stage of the gland is present at birth and is then associated with anencephaly, so that it has been thought that the cortex is in some way connected with the development of tissues rich in lecithin.

APPLIED EMBRYOLOGY

In point of time the cells of the adrenal cortex can be recognized about the fourth week and are derived from the same mass of cells, the genital ridge, which also give rise to either the testis or the ovary. There is thus a common origin for the cortex and the sex gland. The determination of sex takes place about the seventh week, and, as has been noted, the appearance of the fuchsinophilic reaction commences from two to four weeks later.

Crew¹⁶ stated: "That so far as is known, the sex chromosome mechanism is the sex determining mechanism, but in many cases this mechanism can be overridden and the sex of the individual determined in other ways." It is therefore reasonable to argue that a strong and prolonged male phase in the female fetus may possibly be one of those factors which modify sex. To what extent is still a matter of conjecture. A positive reaction has been found in a case of true hermaphroditism, and it is probable that sex reversal, from female to male, will come to be included in this category. But it is known that the cells of the adrenal cortex still retain the power of developing this substance into adult life and that it may become activated at certain periods of physiologic stress, such as puberty. If this explanation is accepted, it readily accounts for groups 1 and 2, which have already been considered clinically.

However, in group 3 the problem is not so simple. It may be argued that in adult virilism there is a failure on the part of some feminizing influence to counteract the male phase. The brief duration of this male phase in the female fetus suggests that it is suppressed, and this suppression is due to some mechanism dependent on the functional activity of the other endocrine organs. That there is some such mechanism was found by Dr. Vines in two female fetuses, in which a prolonged male phase was accompanied by a definite hyperplasia of the pituitary gland. Hence virilism may be due to a failure to maintain the normal restrictive action of the pituitary gland on the masculating potentialities

16. Crew, F. A. E.: Sex Determination. London, Methuen & Co., Ltd., 1933

Summary of Data on Cases of Virilism

Group	Case	Age	Date	Degree of Virilism	Menstrual History	Outlook	Genitalia	Adrenal Removed	Fuchsin Reaction	Result
1	1	15	9/27	Marked	Primary amenorrhea	Normal	Infantile uterus	Left	Strong	Very slight change; abroad
1	2 (figs. 1, 2, 3 and 4)	22	9/23	Very marked	Primary amenorrhea	Indifferent	Infantile uterus; cystic ovaries	Left	Strong	Very slight change; complexion clear with depilation
3	3 (figs. 16 and 5)	18	10/30	Slight	Amenorrhea for 13 mo.	Childish	Infantile uterus; cystic ovaries	Right	Strong	Loss of hair; no change
2	4 (fig. 9)	21	6/29	Moderate	Amenorrhea for 10 mo.	Normal	Small uterus	Left	Strong	Good result; loss of hair; periods regular; married and had a son since operation
2	5 (figs. 7 and 8)	22	10/30	Marked	Irregular periods	Normal	Small uterus; cystic ovaries	Left	Strong	Menses regular; hair less; coming out; headaches less severe; friends remarked on improvement; more feminine
2	6 (fig. 6)	23	7/31	Moderate	Amenorrhea for 1 yr.	Normal	Small uterus; cystic ovaries	Left	Strong	Good; periods fairly regular; hair not coming out so easily as at first; more interested in life
2	7	21	3/32	Moderate	Regular periods	Normal	Infantile uterus; cystic left ovary	Right	Strong	Periods regular; happier; good; complexion clear; no hair
2	8	29	6/32	Slight	Amenorrhea for 9 mo.	Homosexual	Infantile uterus; cystic ovaries	Left	Moderate	Not much change; bedridden before and after operation; has had four periods since; died in 1936; cause unknown
2	9	20	7/32	Moderate	Irregular periods; amenorrhea at times	Normal	Infantile uterus; cystic ovaries	Right	Moderate	Hair comes out easily; periods regular; outlook improved and changed to normal; married recently
2	10	18	8/32	Moderate	Late onset; irregular periods	Indifferent	Infantile uterus; cystic ovaries	Right	Strong	Hair comes out easily; periods regular; more feminine in outlook
2	11 (fig. 11)	30	4/33	Marked	Regular periods	Normal	Small uterus; fibrous ovaries	Left	Fairly marked	Good; hair white at ends, pulls out easily; periods regular; complexion improved
2	12	33	5/33	Moderate	Amenorrhea at 26	Male tendencies	Small uterus; big cystic ovaries	Left	Strong	Amenorrhea continues; brighter outlook; much the same; fair

2	13* (fig. 10)	32	11/33	Moderate	Regular periods; ceased at 20	Homosexual	Small fibroma in uterus; small cystic ovaries	Left	Fairly marked	Period started 2 days after operation; hair all out in 2 wk.; periods normal; psychology now normal; very good result
2	14	26	8/33	Moderate	Irregular periods; ceased at 20	Homosexual	Infantile uterus; cystic ovaries	Left	Moderate	Hair coming out; periods regular; outlook brighter and more normal; very good result
4	15*	54	10/33	Slight	Hysterectomy and right ovariectomy at 33	"Disgusted" with herself; sensitive	Remaining left ovary cystic	Left	Moderate	Hair all out in 2 wk.; slight growth on head; in statu quo
2	16	28	5/32	Moderate	After 21 less and less	Indifferent; prefers men; does not like marriage	Fibroid tumor in uterus; left ovary large; both cystic	Right	Strong	Marriage difficult; improved
2	17	19	3/34	Moderate	Period every 9 mo.	Fond of girls	Infantile uterus; large cystic ovaries	Right	Strong	Increased heterosexual; improved
2	18	40	7/31	Slight	Period every 23 days for 3 days; scanty	Disinterested in opposite sex	Fibroid tumor in uterus; right ovary normal	Left; weight 7.4 Gm.	Strong	Hair gone; periods regular
2	19 (fig. 12)	21	4/35	Marked	At 12 period irregular; amenorrhea 2-10 mo.	Normal	Small uterus; small cystic ovaries	Left; weight 1.4 Gm.	Strong	Periods normal; free from hair; heterosexuality increased
2	20 (fig. 13)	29	6/35	Moderate	Regular periods; 3-4 days every 28 days	Reserved and nervous	Small uterus; fibrous cystic ovaries	Right; weight 6.8 Gm.	Moderate	Satisfactory; face clear
2	21 (fig. 14)	29	8/35	Moderate	Irregular periods	Homosexual	Small uterus; cystic ovaries; luteal cyst	Right; weight 5 Gm.	Strong	Periods improving; less hair; no psychology change
2	22 (fig. 15)	40	9/35	Slight	Irregular periods for 10 yr.; regular for 15 yr.	Heterosexual	Small uterus; ovaries fibrotic	Right; weight 5.8 Gm.	Strong	Periods regular; moustache clear; increased heterosexuality

* Married.

of the female adrenal gland. This type would be associated with a dysfunction of the pituitary gland, the clinical picture being determined by the predominance of one or other factor, and when this dysfunction is in the ascendancy there is a shift toward the type of basophil syndrome of the pituitary gland described by Cushing.

CLINICAL SUMMARY

From an examination of over sixty cases of virilism of varying degree, a few general conclusions may be drawn. That heredity plays a part there is no doubt. A family history of hirsutism was present in 25 per cent, and in these it was twice as common on the distaff side. On the male side it ranged from grandfather, father to brothers; on the female, from mother, sisters, aunts, daughters and nieces, being more frequent in the aunts and sisters. It thus appears to be transmitted more on the female side. There is slight evidence that it is associated with the events which occur at birth. It occurred in two cases of twin births and in one case of premature birth, and in one case it appeared in the 4 year old daughter, within three months of its onset in the mother. With regard to other endocrine disturbances, it appeared in several persons whose mothers suffered from exophthalmic goiter, and in one whose mother suffered from diabetes. In case of mild virilism there were symptoms of hyperthyroidism. One point of practical importance must be stressed, and that is that women with virilism are comparatively infertile, as one would expect from the nature of the pathologic process. If they conceive, they are apt to miscarry. On the other side, one patient on whom unilateral adrenalectomy had been performed and who suffered from amenorrhea has since married and produced a son.

CONCLUSION

A series of twenty-three cases of virilism are presented in which unilateral adrenalectomy was performed without a fatality. We have found a specific differential staining reaction in the cells of the adrenal cortex, which is absent in controls. It is also present in the tumor cells in cases of virilism due to neoplasm. This stain has been verified, and its presence shown in the opposite adrenal gland at autopsy by others. This stain is present in the fetus of both sexes, and virilism can be explained by its abnormal persistence in the female. In some of our patients we have observed an increased amount of cholesterol in the blood. We cannot say what the significance of this stain is. It is associated with definite changes in the growth and development of the body tissues, which have reverted to normal after unilateral adrenalectomy. In some cases it has been associated with alterations in the psychological outlook of the patient, which have reverted to normal after operation.

The same changes have been observed in arrhenoblastoma of the ovary. Cases of pubertas praecox are cited to show that lesions of the hypothalamus are associated with the premature onset of puberty and may be accompanied by psychologic changes. These effects are gonadotropic, of the isosexual type, occurring in children.

This advance in knowledge is all of recent origin, and lies rooted primarily in the fertile soil of surgery. With careful observation by the clinician and close investigation by the pathologist and biochemist and by intelligent cooperation in the study of the rare and limited material, one may now hope that with wider application these tender bulbs may sprout and yield a richer harvest.

Figures 1, 2, 3, 4, 5, 7 and 8 have been published in the *British Journal of Surgery* (19:557-570 [April] 1934) and in "Post-Graduate Surgery" (Rodney Maingot, editor, New York, Appleton-Century Company, Inc., 1936, vol. 2). Figure 11 has been published in the *Lancet* (1:830 [April 21] 1934) and in "Post-Graduate Surgery," and figure 16 was redrawn from a chart which appeared in the same issue of the *Lancet*. Figures 6 and 9 have appeared in "Post-Graduate Surgery." Figures 17, 18, 19 and 20 have been published in "The Adrenal Cortex," by Broster and Vines (London, H. K. Lewis & Co., Ltd., 1933), and in "Post-Graduate Surgery."

XANTHOSARCOMA OF THE CHEEK SUCCEEDING XANTHOSARCOMA OF THE FOREARM

MULTIPLE TUMORS VERSUS METASTASIS

FRED D. WEIDMAN, M.D.

PHILADELPHIA

While xanthosarcomas are rare, there are weightier reasons for making this report. The occurrence of two widely separated tumors was responsible for a consideration of (1) the problem of metastasis (involving the question of genuine malignancy) versus pluricentric tumors and (2) complex problems of internal medicine ranging from the embryologic, developmental aspects of tumors of the acoustic nerve to the diversified changes that may occur in tumors incidental to hypercholesteremia.

Thus, with xanthomatous tumor-like masses occurring (1) in granulation tissue (Garrett¹), (2) in diabetic and pseudodiabetic conditions (Weidman and Schaffer²), (3) with adenocarcinoma of the stomach, (4) with adenocarcinoma of the duodenal papillae, (5) with strictures of the bile ducts, (6) with acute pancreatitis and (7) with hydatid cysts, the attention of the surgeon must be drawn to the field of disturbed general lipid metabolism, which most of the lesions just mentioned can connote.

In short, it is no longer sufficient to view the yellow tumor of tendons and subcutaneous parts simply in a prognostic light; it is incumbent on the physician to distinguish between the yellow color due to blood pigment and that due to lipoid which is part of a true xanthomatous change. In the case of the latter, a broad field of internal medicine opens up, inviting the cognizance of the surgeon as well as of the pathologist, internist, pediatrician, laryngologist and ophthalmologist.

It is of much less importance that the knowledge that lesions occurred on the hard palate and elsewhere in the mouth of the patient whose case I am reporting may prove useful in the differential diagnosis of oral conditions in which perhaps an obvious primary focus is lacking. Still, the proximity of tumors of the acoustic nerve (occasionally xanthomatous) to the vault of the pharynx and mouth may bring the diagnosis

From the Laboratory of Dermatological Research, University of Pennsylvania and the Pennsylvania Hospital.

1. Garrett, C. A.: Tumors of the Xanthoma Type, *Arch. Surg.* 8:890 (May) 1924.

2. Weidman, F. D., and Schaffer, H. W.: Xanthoma of the Skin and Larynx, Associated with Carcinoma of the Stomach and a Regressive Xanthoma of the Pons, *Arch. Dermat. & Syph.* 35:767 (May) 1937.

of oral conditions into the realm of such important states as intracranial tumors. Indeed, such a consideration was brought up by the studies on my patient.

REPORT OF A CASE

History.—Bessie H., aged 34, a Negress, was admitted to the Pennsylvania Hospital on June 7, 1924, on account of a large tumor on the right arm. It was the size of a grapefruit, apparently extended upward from the ulna to the humerus, and was firmly fixed to the underlying parts. The radius and ulna were adherent to each other: it was scarcely possible to flex or to extend the forearm.

The mass of the tumor extended definitely above the general cutaneous level; while it was not ulcerated, the skin was excessively thin, and its surface was made up of such numerous, shallow lobulations that there was a close approach to a fungoid form. In view of the dark color of the Negress, the intrinsically yellow color of the tumor was not recognized clinically, and the xanthic phases in the case were not identified until pathologic examination.

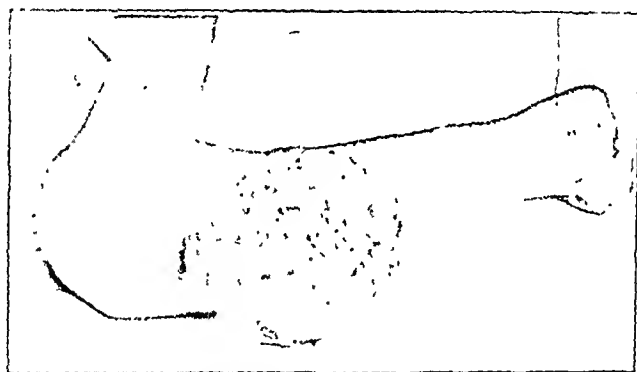


Fig. 1.—Xanthosarcoma of the forearm.

In 1913 the patient received a blow on the right forearm; succeeding the contusion, a tumor developed slowly. In seven years it became as large as an apple; subsequently it grew more rapidly. At times neuralgic pains extended down the arm. The patient lost 35 pounds (15.9 Kg.) from 1921 to 1924.

Physical examination did not disclose evidence of metastasis, except for an exostosis of the right malar bone. The mouth was examined carefully. The roof was high, and the teeth were in fair condition; certainly there were no metastatic lesions in the mouth at that time. From the clinical examination of the chest the possibility of pulmonary tuberculosis was considered. However, roentgen examination did not confirm this suspicion.

On admission the liver and spleen were not palpable, nor were there any other palpable masses in the abdomen. The uterus was slightly enlarged, but there were no palpable masses.

Roentgenograms of the accessory nasal sinuses showed only a slight cloudiness over the right antrum. A roentgenogram of the right arm showed that the lower third of the humerus and the upper three fourths of the radius and ulna were involved; there was destruction of the bone, as well as evidence of attempted regeneration. This resulted in marked deformity, particularly of the radius and ulna. In one place the two bones were particularly deeply eroded. Practically all trace

of the medullary canal was lost. The density of the bone varied irregularly from place to place. The roentgenologist confirmed the diagnosis of sarcoma, and was of the opinion that the bone had become involved secondarily.

Clinical Summary.—Following a contusion of the forearm, a tumor developed slowly for seven years; in the succeeding four years it developed more rapidly. The large size and the evident infiltrative and destructive propensities of the lesion justified the diagnosis of sarcoma, which was confirmed roentgenologically. No metastases were apparent, but an enlargement on the malar bone was noted which subsequently proved to be xanthomatous (and probably also xanthosarcomatous).

Pathologic Examination.—Following amputation 4 inches (10.16 cm.) below the head of the humerus the specimen was dissected and the extent of the infiltration by the tumor was determined. Loose polyps of tumor tissue were found infiltrating, but not eroding, the cavity of the joint; spaces in the lower third of the forearm were also infiltrated. The muscles of the forearm and also the posterior group of muscles of the upper part of the arm were almost completely atrophied. The osseous tissue was markedly changed; the humerus was perforated, and there was a small round cavity, 2 cm. in diameter, just above the epiphysial line. The cavity showed a smooth wall lined by tumor tissue, which also extended into the medullary cavity. The radius and the ulna showed considerable absorption of bone salts. At the distal end of the humerus, tumor tissue was found infiltrating the medullary cavity.

Histologic Observations.—Ten blocks of tissue were selected from different parts of the tumor in order to gain as representative a picture as possible of the entire composition of the growth. It was desired particularly to determine the presence or absence of necrosis; hence those parts which seemed softest or hemorrhagic were selected. In no case was a focus of necrosis found in any of the blocks of tissue.

Tendons: Two sections were taken from the wrist and one from the upper part of the arm. The only abnormality consisted in an extremely slight hyperplasia of the cells lining the sheath.

Fungating Portion of the Lesion: This section consisted chiefly of whorling strands of young fibrous tissue—typical fibrosarcoma. From place to place small giant cells occurred and also xanthoma cells. This fibrosarcomatous part blended imperceptibly with the corium and even the papillae of the skin. In the deepest parts of the section the cells were extremely xanthomatous, cytoplasm being fused to produce smaller and larger areas of pink granular material in which the nuclei of the xanthoma cells still persisted. Probably 80 per cent of this large section exhibited fibrosarcomatous (no xanthoma) features, while the remainder consisted either of large, more or less polyhedral cells (swollen fibroblasts) or xanthoma cells.

Uppermost Portion of Tumor (Infiltrating): Two sections were submitted. There was a definite fibrous capsule around one section. The tumor consisted exclusively of large, more or less polyhedral cells, many of which were xanthomatous. Fibrosarcomatous characteristics were exhibited only in small and widely scattered areas, although here and there were some remnants of an original stroma of fibrous tissue. Giant cells were numerous. These characteristics were repeated in the second block of tissue selected.

Interosseous Membrane: There was only a suggestion of sarcomatous change, thus suggesting that the nuclei of fibrous tissue cells were moderately hyperplastic in some positions. The most striking feature was the extraordinarily broad and

dense accumulation of lymphoid cells around the blood vessels. Such cells did not tend to xanthomatous change, although spindle cells in their immediate proximity exhibited such a change. Plasma cells were widely infiltrated throughout the section. They did not tend to xanthic change. Skeletal muscle fibers were atrophic; their cytoplasm was rarefied and suggested xanthomatous change. Their nuclei were tremendously hyperplastic.



Fig. 2.—The postoperative specimen. Samples of tissue were taken from ten portions of the tumor to test the lipid partition of the fats: 1, the interosseous fibrous tissue; 2, the most central parts of the tumor; 3, the summit of the fungus growth (superficially ulcerated); 4, the fibrous capsule; 5, the central portion of the tumor; 6, areolar fat; 7, muscle; 8 and 9, the peripheral advancing part of the tumor, and 10, a portion at the junction of the fibrous center and the definitely xanthomatous part.

Skin of the Wrist: Two sections were submitted. In one there were no xanthomatous features; the nests of xanthoma cells which Kreibich³ reported in grossly normal skin of a diabetic patient with xanthoma were not repeated here. In the second section the deepest parts of the skin were heavily infiltrated by lymphoid cells, particularly the subcutaneous fat. There was definite fibrous hyperplasia in the deepest parts of the subcutaneous tissue, together with a minor formation of xanthoma cells. However, the true skin was free from xanthomatous foci, as was the first section.

Likewise, sections of normal skin from the back of the hand and the palm failed to disclose xanthomatous foci.

The Intramuscular Nodule: This was selected for study with the idea that it would represent tumor processes in their earliest stage, i. e., in the most outlying and detached portion of the entire tumor. Again dense infiltrations of lymphoid



Fig. 3.—Roentgenogram illustrating the erosion of the bones.

and plasma cells around the blood vessels were noted. Skeletal muscle fibers had lost their transverse markings and had become so disorganized as to simulate white fibrous tissue. The tumor cells were predominantly spindle shaped, and there were comparatively few xanthoma cells. The matrix of fibrous tissue between the cells was dense and abundant.

Frozen Sections: The xanthoma cells were found to contain neutral fat almost exclusively when stained by sudan III. Crystals could be recognized only from place to place, sometimes in comparatively large masses. They stained red indifferently compared with the neutral fat. With polarized light only a portion of the crystals was found to be doubly refractive. A source of error consisted in the presence of certain globules of neutral fat which lay in a plane immediately

3. Kreibich, C.: Zosteriform Xanthoma, *Arch. f. Dermat. u. Syph.* 152:365 (Dec. 3) 1926.

above the doubly refractive crystals; under these circumstances such crystals appeared to be red. The error was eliminated photographically by the use of a blue screen, which gave a truer quantitative photographic registration of the doubly refracting substance by blocking out the "contaminating" red (neutral fat) factor.

Summary and Comment.—The more peripheral, presumably advancing parts of the tumor showed characteristics of fibrosarcoma; the xanthomatous changes appeared in the older, more central regions. As

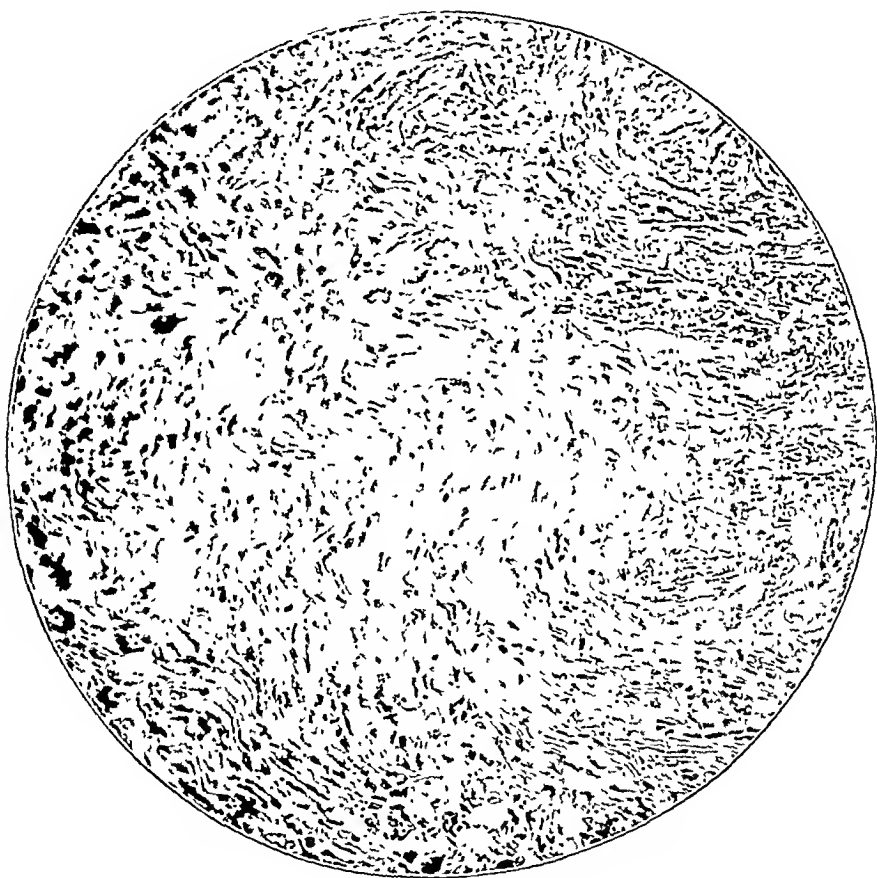


Fig. 4.—Xanthosarcoma of the forearm: the fibrous portion, showing evidence of the fundamentally fibrous nature of the tumor.

transitions from spindle and polygonal cells into xanthomatous cells could be traced (best in the peripheral position), it appeared that the tumor was essentially a fibrosarcoma and that the xanthomatous changes had been superadded. The lipids concerned appeared to be overwhelmingly neutral fats; it was assumed that the doubly refractive ones represented cholesterol. Incidentally, the latter type of lipids tended to occur in masses. Since they were not recognizable in individual cells, it was assumed that they occurred not as part of the essential metabolism of

the xanthoma cell but as a secondary development. However, I have no idea what processes are involved in this secondary development.

SECOND OBSERVATION OF THE PATIENT

The patient was discharged with a completely healed wound three weeks after operation. Five months later she was readmitted to the hospital on account of swelling on the right side of the face and deafness. At three places, i. e., over the

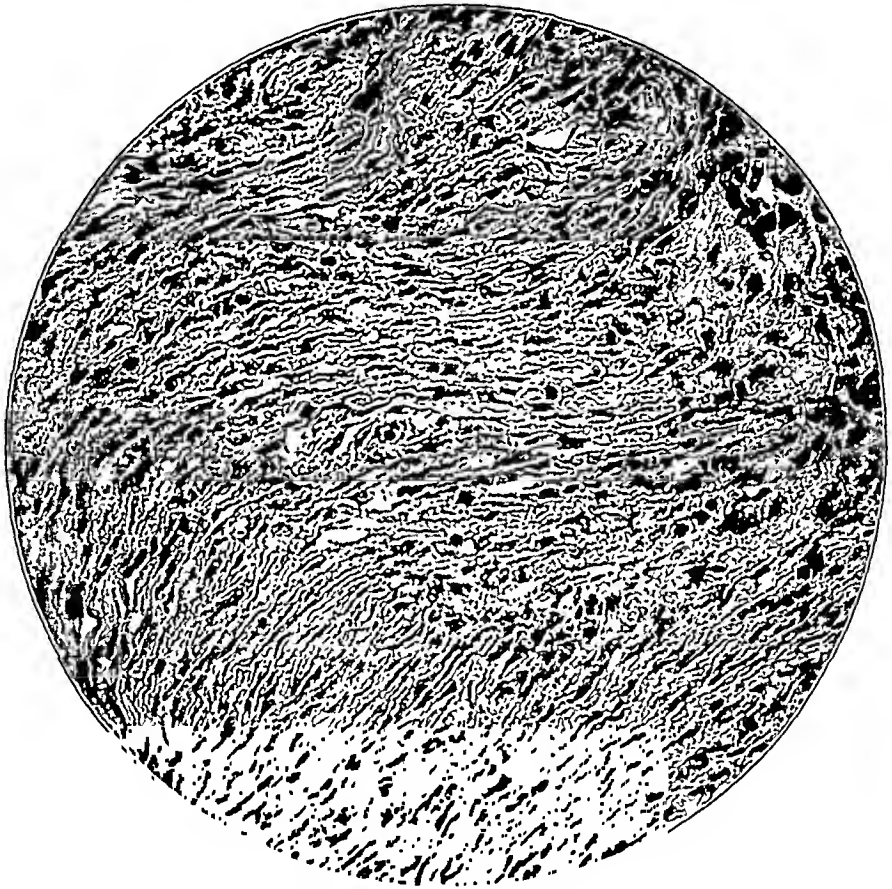


Fig. 5.—Xanthosarcoma of the forearm: the fibrous portion, showing early lipid change (many minute vacuoles).

right maxilla, in the region of the upper antrum and posterior to the right ear, there were four sessile growths, varying from 3 mm. to 8 cm. in diameter. Except for the lesion first mentioned, they were adherent to the overlying skin, which was hyperpigmented, thus preventing recognition of any yellow color.

However, a yellowish brown color was noted in the nodules in the mouth. These were most numerous over the upper right alveolar ridge; in particular, a polypoid extension protruded outward from the interval once occupied by a molar tooth, and attracted attention to this location as a likely center for the entire

process. Furthermore, there appeared to be a definite fulness of the immediately underlying parts. The nodules were movable, hard and of irregular size and shape. Some were discrete, while others were confluent, forming larger masses.

The nose did not appear to be involved. The air passages seemed to be free; there was no discharge, and the mucous membranes appeared normal. The external auditory canals were clear. There were no gross ocular symptoms, such as exophthalmos, palsy or ptosis. No softening or thickenings could be detected on the cranium; it was of normal shape and circumference.

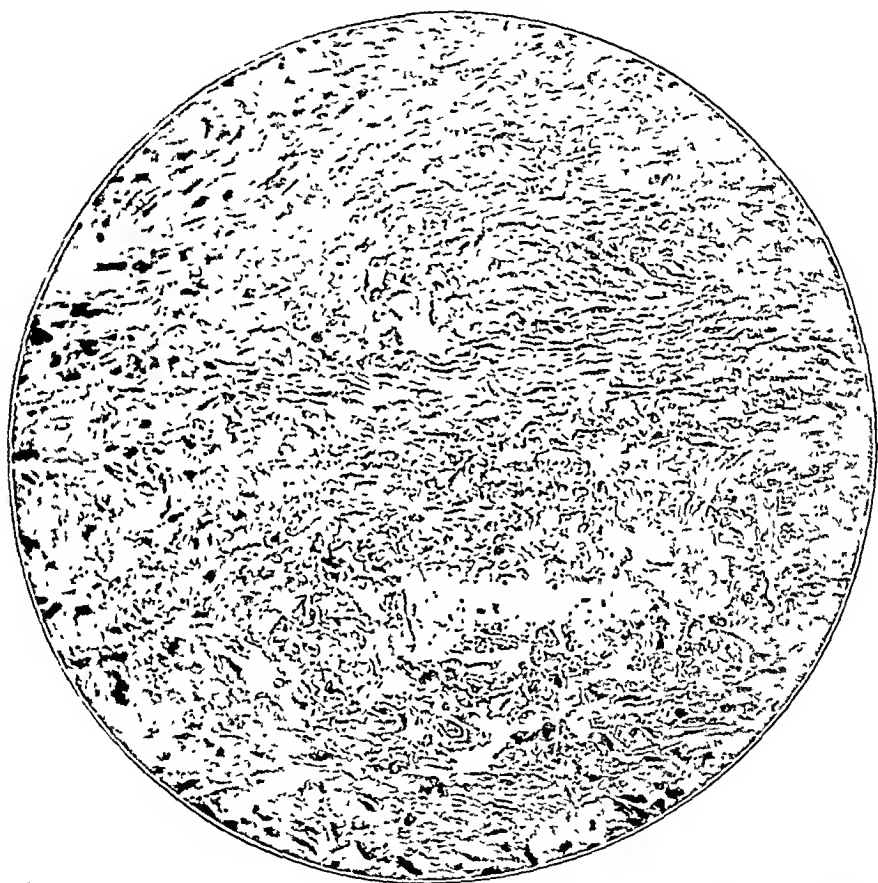


Fig. 6.—Beginning transformation of spindle cells, in the bundle immediately above the equator, into xanthoma cells just below.

The mass over the right maxilla was not adherent to the skin but was definitely incorporated with the maxilla. In the buccal wall immediately subjacent, a hard mass could be shifted about with ease; it measured 1.5 by 0.75 by 0.50 cm. It appeared from this fact that the mass occupied the antrum and adjacent tissues, even as far as the cutaneous and oral mucosa.

No nodules were visible on the vaginal and cervical mucosa.

Physical Examination.—Skin: The patient stated that subsequent to the operation certain old scars became elevated and itchy. One such scar, on the right side of the chest anteriorly, was definitely lemon yellow and elevated. (A specimen

was removed for biopsy; while the lesion had not resembled keloid clinically, the pathologist reported only a subcutaneous fibrosis, with no foam cells or other lipid deposition.)

Abdomen: There was now fulness in the flank owing to a questionable small amount of ascites (not present at the first admission), and the liver was palpable; no bosses were felt on the surface. Otherwise no abnormalities were detected.

Eyes: No crystals (referable, for instance, to deposits of cholesterol) were recognizable. The internal examination gave normal findings.

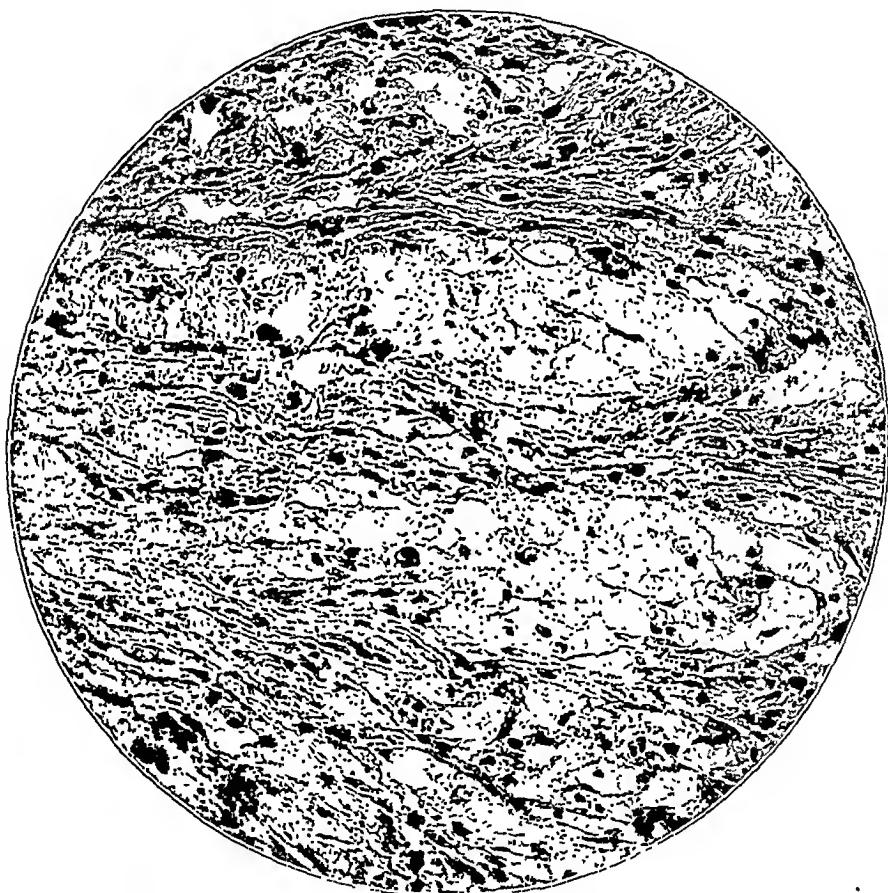


Fig. 7.—Xanthosarcoma: section illustrating the close relationship between fibrous tissue and the xanthoma cells.

Laboratory Examinations.—The cholesterol of the blood measured 177 mg. per hundred cubic centimeters; the sugar, 90 mg.; the urea nitrogen, 68 mg., and the uric acid, 3 mg.

Examination of the urine failed to reveal anything abnormal. The Wassermann test of the blood gave negative results with both cholesterolized and noncholesterolized antigens. The blood count revealed: hemoglobin, 58 per cent; red blood cells, 3,080,000; white blood cells, 5,200, and a differential count of 59 polymorphonuclears, 40 lymphocytes and 1 basophil.

Roentgen Examination.—Stereoscopic roentgenograms of the accessory nasal sinuses, taken both laterally and anteroposteriorly, did not give evidence to substantiate the diagnosis of xanthosarcoma.

The consulting otolaryngologist found extensive infiltration around the right side of the fauces, probably causing occlusion of the eustachian tube. The mucous membranes of the tympanum were markedly retracted as a result of the occlusion of the eustachian tube, accounting for the deafness.

Course.—The patient was given a diet poor in cholesterol for several days. The cholesterol value of the blood after two days of this regimen was 132 mg. per hundred cubic centimeters.

As the condition was inoperable, the patient was discharged. With the amputated specimen, she was presented before the Philadelphia Pathological Society in January 1925.⁴ It has not been possible to determine the subsequent course of events except that she moved to a distant state and later died. Necropsy was not performed.

SUMMARY AND COMMENT

In general, the lesion of the arm followed the conventional course of xanthosarcoma; that is, it succeeded trauma, grew slowly and probably began in the tendon sheaths. In all these respects it conformed to fibrosarcoma. It is likely that the lesion was essentially a fibrosarcoma, with a superimposed or concomitant cholesterol infiltration of the tumor cells. Metastasis to such a solitary area as the facial bone must arouse skepticism as to the genuineness of a sarcomatous phase in the facial lesion. With a knowledge of the propensities of the bones to become involved in other expressions of the hypercholesteremic diathesis (Christian's disease), it is reasonable to wonder whether the facial lesions were purely xanthomatous and not necessarily xanthosarcomatous. The apparent absence of visceral metastasis does not help toward a decision, for the relatively benign habits of fibrosarcoma and xanthosarcoma would permit the presence of such small lesions in the lungs and liver that they could not be recognized until necropsy. However, the comparatively rapid progress of the facial swelling and the multiplicity of nodules of the skin of the face and oral mucosa gave stronger evidence for sarcoma in the facial lesions than any other presented.

The manifestations in the cholesterol were not convincing. A value of 177 mg. per hundred cubic centimeters may be regarded within the normal limits, and the second figure obtained, i. e., 132 mg., is even below the lower limit of normal. This would suggest that cholesterol-producing processes were not present when the sample of the patient's blood was taken. (There is evidence that there may be periods during which waves or surges of cholesterol occur in the blood stream, as in untreated diabetes and pregnancy and at the climacteric.) That this

4. Sunderman, F. W.: Xanthosarcoma, *Proc. Path. Soc. Philadelphia* 27:88 (Jan.) 1925. Dr. Sunderman followed the clinical course of the patient.

possibly was true is suggested by the patient's testimony that during a pregnancy which developed two years after the beginning of the tumor, multiple yellow tumors appeared over the entire body. She stated that at that time there were masses on the uterus and that a cesarean section was performed.

In any event, it is clear that extensive xanthomatous infiltration can take place in the mucous membrane of the mouth and in the underlying tissues of the face independently of coincident cutaneous manifestations. This case is also an example of the possibility that xanthomatous lesions can exist in the absence of hypercholesteremia.⁵ However, this does not exclude the possibility that hypercholesteremia might still occur intermittently, the xanthomatous lesions persisting during the remissions owing to the slow absorption for which cholesterol is noted.

MALIGNANCY IN XANTHOSARCOMA

In a consideration of the malignancy of xanthosarcoma generally there are difficulties if one confines oneself merely to abstracts of the literature on the subject, such as those of Tourneaux⁶ and Krogius.⁷ Broders'⁸ report of seventeen cases, in which he stressed benignancy in "benign xanthic extraperiosteal tumors of the extremities," while suggestive, does not bear strictly on the subject of sarcoma. Each of the seventeen lesions contained lipids and blood pigment; since Broders was not concerned with the general systemic lipoidal phase of the situation he did not state whether the yellow color was referable more to fat or to blood pigment. However, since he emphasized trauma, old hemorrhage and blood pigment in sections, and since foam cells were present in only 64 per cent of the cases, it is clear that he used the term "xanthic" in the objective rather than in the pathologic sense, i. e., not necessarily "xanthomatous." In his opening sentence Broders said, "pertaining to, or tending toward a yellow color."

But even omitting Broders' cases as instances of sarcoma the impression still exists that xanthosarcomas, like all tumors of the tendon sheaths, are relatively benign, to which I agree. However, Krogius challenged this opinion; he believed that, while xanthosarcomas are admittedly at a

5. Schaaf, F.: Metabolism of Lipids, *Zentralbl. f. Haut- u. Geschlechtskr.* **35**:193, 1930.

6. Tourneaux, J. P.: Sarcoma of the Tendon Sheaths, *Rev. de chir., Paris* **47**:817, 1913.

7. Krogius, A.: Xanthosarcomas in Tendon Sheaths, *Finska läk.-sällsk. handl.* **64**:102, 1922; abstr., *J. A. M. A.* **79**:173 (July 8) 1922; *Acta chir. Scandinav.* **55**:363 (Dec. 22) 1922.

8. Broders, A. C.: Benign Xanthic Extraperiosteal Tumor of the Extremities Containing Foreign-Body Giant Cells, in *Collected Papers of the Mayo Clinic*, Philadelphia, W. B. Saunders Company, 1919, vol. 11, p. 1032.

low level of malignancy, they are not so strictly limited neoplastically that they do not metastasize. Thereupon I analyzed the original reports of cases in the light of the pathologic, and particularly the histopathologic, examination, the results of which are presented later. Krogius complicated the situation at the outset by including not only fibromas of the extremities but also a myxosarcoma, and as his report has been abstracted in American literature, there is an additional reason why the relations between xanthoma and xanthosarcoma should be reexamined in order to correct any erroneous impression that may have arisen.

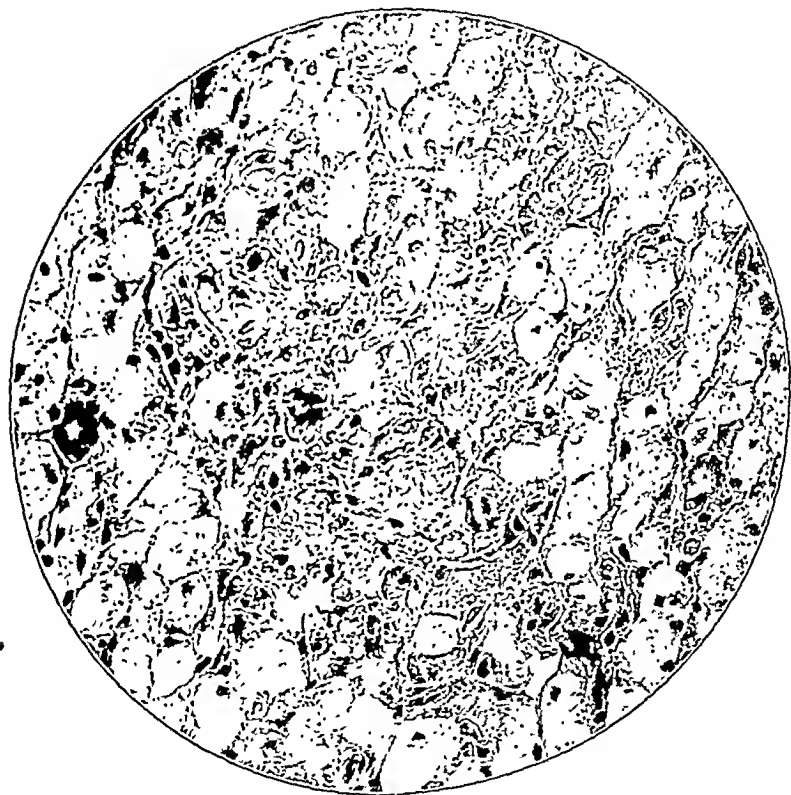


Fig. 8.—Xanthosarcoma: section illustrating nonxanthomatous giant cells and their source in fibrous tissue cells. The formative cell in the circle still shows a cloddy, comparatively nongranular type of cytoplasm which bespeaks its connective tissue composition.

To begin with, Krogius' own series of five cases included but one instance of recurrence; there were no metastases. In his survey of the literature, he cited Tourneaux's compilation of ninety-three cases, leaving the impression that Tourneaux was reporting xanthosarcomas. Reference to the original publication discloses, however, that Tourneaux

did not mention "xantho" in his entire article. Furthermore, in his histologic report he did not describe cytoplasmic degenerations or indicate any in the illustration which would suggest xanthomatous phases.

However, conceding that histologic limitations of Tourneaux' (1913) report did not exclude xanthomatosis, it is most doubtful if any of the growths were xanthosarcomas. Tourneaux collected reports of six instances of metastasis; incidentally, Harbitz⁹ also, in turn, cited them. However, on consulting the original communications, of which only three were available (Tourneaux' references are inadequate), it was found that they did not bear out the claim that even nonxanthomatous fibrosarcomas metastasize. Thus, referring to the metastasis in his case, Bolognesi¹⁰ stated no more than that "one year later his brother advised us of his death from a malignant disease with vomiting of blood, extreme weakness, and yellow discoloration of the skin." This is anything but convincing that xanthomatous disease in the lungs was the cause of the vomiting of blood, particularly if jaundice was present. The patient may have had esophageal hemorrhoids.

The report from the Heidelberg Clinic¹¹ was in telegraphic style; its extent was two lines: "Myxosarcoma of fascia lata. Extirpated. Three months later inoperable recurrence and metastasis to lungs." Myxosarcoma is far removed from xanthosarcoma.

The third citation was an obvious clerical error. All that Degorge¹² stated was that "the patient was seen recently and does not show any recurrences." The tumor was a "fusocellular tumor with giant cells." Tourneaux' ninety-three cases, then, lamentably fail on close analysis to reveal a single example of authentic metastasis of xanthosarcoma. Furthermore, the inadequacy of the evidence is disconcerting, particularly since the erroneous impressions passed through the hands of Tourneaux, Krogius and Harbitz.

Krogius also cited Gaudiani's¹³ cases of primary sarcoma of tendon sheaths and its widespread metastases. The statements concerning the latter were valid. Histologically, however, I found that the sarcoma did not qualify as xanthosarcoma; the illustrations depicted alveolar spindle cell sarcoma. The histologic picture was the same in the primary tumor of the groin and in the metastases to the myocardium, the skin and the intestines. There were a gigantic lesion the size of an orange on the dura mater and metastases to the iliac and perirenal regions.

9. Harbitz, F.: Tumors of Tendon Sheaths, Joint Capsules and Multiple Xanthoma, *Arch. Path.* 4:507 (Oct.) 1927.

10. Bolognesi, B.: *Globo-Cellular Sarcoma*, Thèse de Paris, 1881, p. 29.

11. Report from Heidelberg Clinic, *Compt. rend. de Clin. de Heidelberg*, 1901, p. 209; 1902, p. 237.

12. Degorge, quoted by Tourneaux.⁶

13. Gaudiani, V.: Primary Sarcoma of Tendon Sheaths: Single Case Report, *Policlinico* 13:547, 1906.

Thus, Krogh's rebellion against the relative benignancy of xanthosarcoma subsides when one analyzes the original reports in the light of xanthosarcoma in its strict sense, and Broders' conclusions as to the relative benignancy of pleosted xanthoma must also apply to xanthosarcoma. Even for fibrosarcoma (nonxanthomatous), the instances of widespread generalization narrow down to the solitary case of Gaudiani. That local metastasis of fibrosarcoma occurs, to the

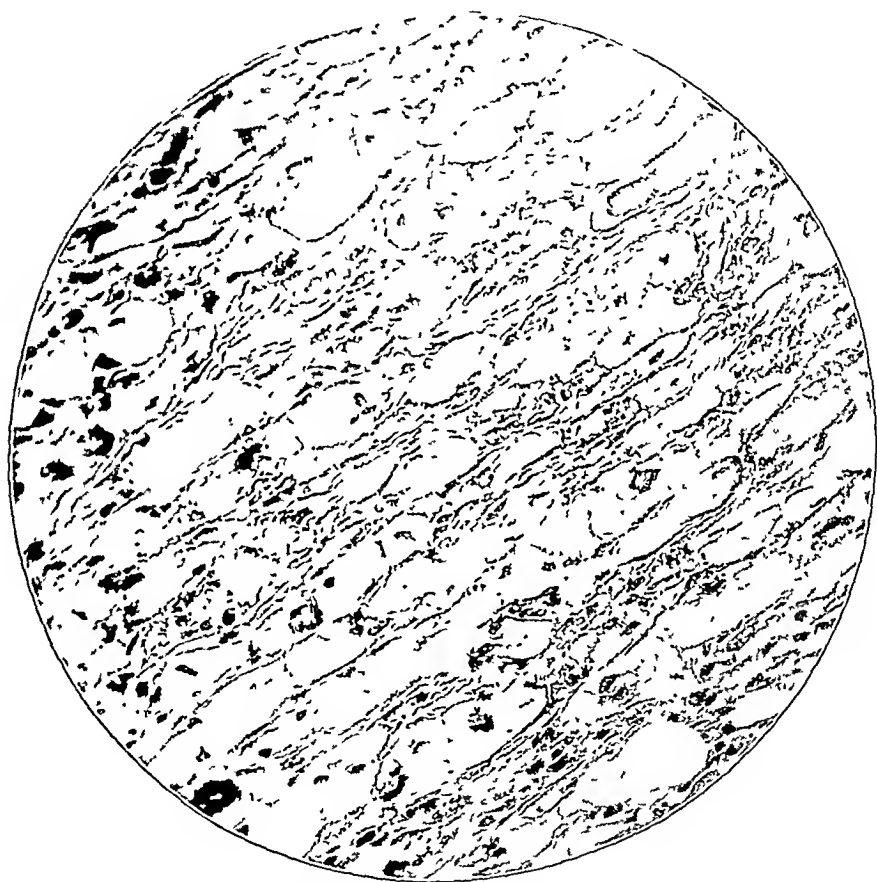


Fig. 9.—Xanthosarcoma section from deeper parts of the "fungus growth" The genesis of xanthoma cells from fibrous tissue cells is illustrated. Their original arrangement as part of the connective tissue bundles is still maintained

extent of regional involvement of the lymph nodes and local recurrence, is conceded. In any event, metastases as distant as from the extremity to the face, as in the case reported here, appears to be unknown heretofore for xanthosarcoma, and is seldom seen in fibrosarcoma, as in Gaudiani's case.

The review of the literature disclosed a further misapprehension Tumors were denominated xanthomatous in the absence of microscopic

examination; the mental reservation should be made in this connection that necrosis, hemorrhage and pigmentation can impart a yellow color to sarcoma. This is important to remember in evaluating the older reports of xanthomatous lesions, and will be elaborated further in respect to modern practice.

Turning from the subject of metastasis to essential malignancy, one may assume tentatively that, contrary to some recent pronouncements, true xanthosarcomas are like fibrosarcomas; locally they are malignant, whether in connection with tendon sheaths or not. They infiltrate and destroy tissue locally and recur on excision, but do not tend to distant metastasis. The lesions in the hard palate of the patient reported here grew so rapidly and were so yellow that they could have been only xanthosarcomas; if this diagnosis is accepted, in the absence of confirmatory histologic examination of the metastatic lesion, I may be recording a case of distant metastasis of xanthomatous sarcoma that is perhaps unique. An alternative (pluricentric) mechanism will be discussed later.

The case of "Xanthofibrosarkom der bursa subachillae anterior" reported by Hünemann¹⁴ was one of the earliest authentic cases; Aschoff saw the sections and confirmed the diagnosis of a giant cell xanthosarcoma. It was "relatively benign, but liable to recurrence." Following local excision it recurred in the scar in four weeks. There was no recurrence after amputation at the middle of the thigh. This may be accepted as the "type diagnosis" of xanthosarcoma. Further clinical details are available in papers by Harbitz,⁹ Bloodgood,¹⁵ Broders,⁸ Krogius⁷ and Kammer.¹⁶ The last mentioned study is probably the classic work of its time, because conducted under the supervision of Aschoff.

Xanthomas of Mucous Membranes.—Tumor-like masses of xanthomatous change analogous to those in the case reported here are very rare in the literature. Only Lebedew¹⁷ described a case which had a resemblance to it. The lesions, which appeared to be granulomas, began in front of the shoulder, extending thence to the face, to the hips, around the waist, on the thighs and around the knees. The largest ones became ulcerated. As to the mucosal involvement, there were yellow nodules in the soft palate sufficiently large to displace the uvula. Lebedew's color plates brought out the reddish yellow qualities of the

14. Hünemann, T.: Ueber einem Fall von Xanthofibrosarkom der Bursa subachillae anterior, Deutsche Ztschr. f. Chir. **182**:410, 1923.

15. Bloodgood, J. C.: Xanthomas, Arch. Surg. **8**:882 (May) 1924.

16. Kammer, E.: Giant Cell Xanthosarcoma, Inaug. Dissert., Freiburg, 1909.

17. Lebedew, A. J.: Xanthoma Multiplex Pseudo-Diabeticorum with Xanthomatous Lymphadenitis, Dermat. Wchnschr. **59**:1343, 1914.

nodules on the forehead, eyebrows and nose and in the mouth. He described the nodules as bluish red at first; later they became yellow in the center. These inflammatory changes were strongly suggestive of the xanthomatous lesions in diabetes mellitus, the dermatologic aspects of which are characteristically different from those of other forms of xanthoma. Lebedew summarized his case as one of a condition simulating xanthoma diabetiforme but without diabetes. The cholesterol concentration of the blood was not reported.

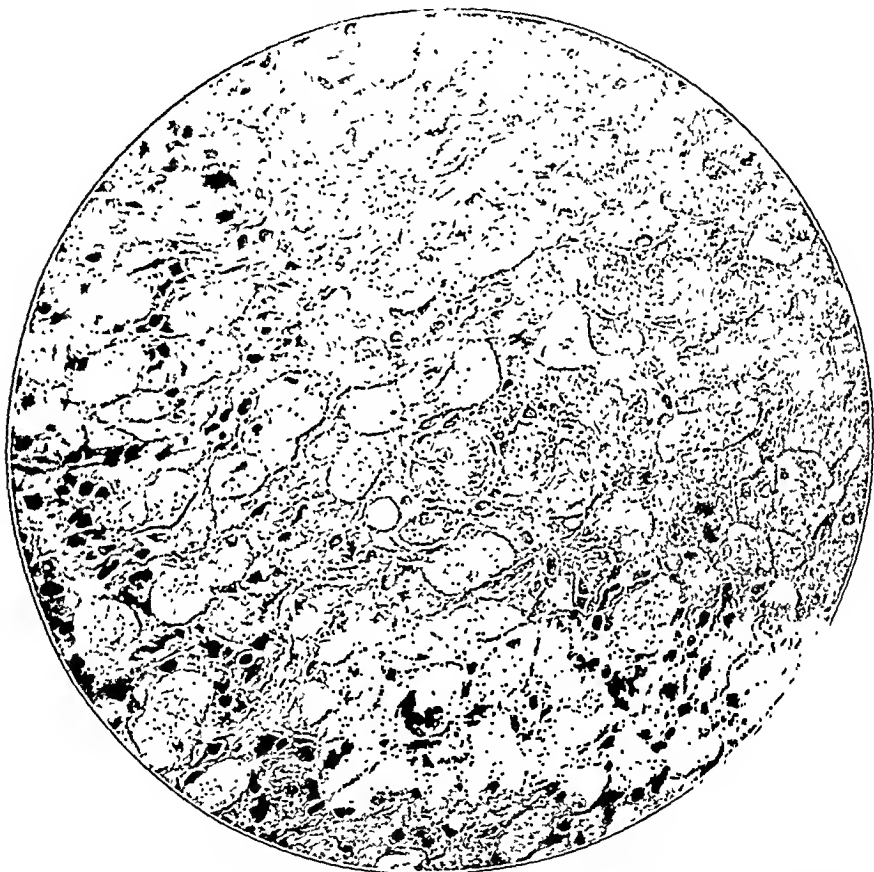


Fig. 10.—Xanthosarcoma: a mixture of mononuclear and multinucleated cells, some in the course of being xanthomatous.

A further instance of xanthoma of the mucous membrane, which came under my observation at necropsy, was a case of involvement of the epiglottis in a man who died of carcinoma of the stomach and a regressive xanthoma in the pons. Previously the lesion had been observed bronchoscopically. This case is reported elsewhere in detail,² with a full compilation of reports of cases of xanthoma of the mucous mem-

brane; more or less diffuse plaques on the gums and hard palate have been observed frequently.

Tumor of the Acoustic Nerve.—This lesion, sometimes cholesteatomatous, occupies the cerebellopontile angle. I have introduced this subject on account of the proximity of my patient's facial lesion to the temporal bone, which is intimately associated with tumors of this nerve. Weidman and Schaffer have abstracted elsewhere² the point of view of the neurologist, including the connection which tumors of the acoustic nerve have with molluscum fibrosum, xanthoma of the skin and neurofibroma of other parts of the body. Obviously these considerations have a direct bearing on the question of metastasis and pluricentric development of tumors, which will be elaborated later in this paper.

In the case reported here, however, an acoustic phase can be eliminated, because roentgenograms showed that the petrous portion of the temporal bone was perfectly preserved; a tumor of the acoustic nerve sufficiently large to have occupied the antrum would surely have invaded its favorite terrain, the petrosa. The major focus of obstruction of bone appeared to be around the root of the last molar tooth on the right side of the upper jaw.

Some General Systemic Aspects of Xanthomatous Processes.—In 1910, when Chauffard¹⁸ and his co-workers announced a hypercholesteremia in connection with xanthomatous changes, a new trend of thought was developed, and up to the last two or three years cholesterol has dominated the subject of xanthoma etiologically. This is not surprising when the blood cholesterol content may increase almost tenfold (to 1,035 mg. per hundred cubic centimeters and more) in a case of xanthoma tuberosum. In such a case the cholesterol, being thus in excess, should be deposited in the cutaneous lesions. It has always been appreciated, however, that other lipids were associated. Weidman and Freeman¹⁹ stated:

All of these bodies have not been demonstrated in every case of xanthoma reported—cholesterol has been infrequently reported on the basis of histologic examination, but on chemical analysis of lesions it appears to be constant. (It should be recalled that cholesterol exists amorphously as well as in crystalline form.) Neutral fats appear constantly. They are readily demonstrated by Sudan III and scharlach R, but usually not by osmic acid; that is, they are not the glycerols of such unsaturated fatty acids as the oleates of normal human fats.

18. Chauffard, A., and Laroche, G.: *Pathogénie du xanthelasma*, *Semaine méd.* 30:241, 1910.

19. Weidman, F. D., and Freeman, W.: *Xanthoma Tuberosum*, *Arch. Dermat. & Syph.* 9:149 (Feb.) 1924.

Recently, however, attention has been called to the blood fats as a group.²⁰ More and more, it is appreciated that the disturbance is one of the entire group of blood fats, and not of cholesterol in particular. Eckstein's conclusion that "the nature of the lipids in xanthoma is more dependent upon the activities of the tissues than upon the nature of the blood lipids" doubtless applies with special force to this case of xanthosarcoma. His statement is probably not so binding in the non-neoplastic xanthomatous infiltrations such as residual abscesses; when considering neoplasia such radically different circumstances are encountered, particularly involving metabolic conditions, that it becomes a duty to discover whether the processes established for non-neoplastic growth and metabolism are still operative.



Fig. 11.—Xanthosarcoma: the fibrous portion, demonstrating the fatty granules within the fibrous tissue cells and the foamy cytoplasm of the giant cells.

Lipoidosis in Malignant Processes.—As a disturbance of fundamental metabolism, little is known of the pathologic interrelationships which are peculiar to lipids as they affect malignant cells. But it is known that neoplasia is essentially a matter of growth and that cholesterol is not alone a constant constituent of all cells but one which affects at least the fragility of red blood cells and, linked with vitamin D, is a pronounced factor in growth. Luden²¹ probably had such thoughts when

20. Wile, U. J.; Eckstein, H. C., and Curtis, A. C.: Lipid Studies in Xanthoma, Arch. Dermat. & Syph. **19**:35 (Jan.) 1929. Eckstein, H. C., and Wile, U. J.: Lipid Studies in Xanthoma, J. Biol. Chem. **87**:311 (June) 1930. Curtis, A. C.; Wile, U. J., and Eckstein, H. C.: Involution of Cutaneous Xanthomata, J. Clin. Investigation **7**:249, 1929. Schaaf.⁵

21. Luden, G.: Studies on Cholesterol: VI. Value of Blood Cholesterol Determinations and Their Place in Cancer Research, Canad. M. A. J. **12**:147, 1922.

she emphasized the place for cholesterol determinations in research in cancer. White²² regarded the cholesterol crystals which he found so abundantly in cancer as the product of the cancer per se and not of secondary degenerative processes. The capacity of cholesterol, too, to augment experimental cancer in rats challenges interest; but one cannot speculate further because the very xanthosarcomas which presumably contain so much cholesterol are not notably malignant.

Partition of Lipids in Xanthosarcoma.—"Partition" refers to estimation of the differing proportions of cholesterol, cholesterol esters, neutral fat, phosphatides and so forth, which comprise the entire group of lipids, a procedure similar to the partition of nitrogen in the urine in relation to its ammonia and urea fractions, which has become a method in medicine. In view of the fact that necroses were not noted in the xanthosarcoma which I studied (nuclear degenerations and liquefaction were absent), it was believed that a fairly close estimate of the basic lipoidal metabolic products of the sarcoma cell could be made.

White contributed information concerning the different lipids in malignant tumors. He found that cholesterol and fats occurred regularly in them. Studying the melting points and the behavior toward polarized light in frozen sections on the warm stage of the microscope, he divided the crystals into five groups. Their composition was as follows: (*a*) cholesterol (almost pure); (*b*) a mixture of cholesterol and fatty acids (and alcohol or lecithin); (*c*) neutral fats (often containing fatty acids); (*d*) mixtures of cholesterol with fatty acids (or lecithin and glycerin, etc.), and (*e*) the same composition as *a*, *b* and *d*, but different in certain details of morphology.

Almost every carcinoma that White examined contained crystals *d* or *e*, sometimes associated with *a*, *b* and *c*. Since they did not occur as a rule in necrotic areas, he concluded that they were associated with the proliferation of cells rather than with their degeneration; therefore "it is suggested that cholesterolin may be associated in some way or other with the regulation of cell proliferation." (Incidentally, Roffo²³ found as much as three times more cholesterol in cancerous tissue than in the rest of the animal. He reemphasized the ability of cholesterol to take up water—something which may mean much in the water and other metabolism of cells.) Crystals *d* and *e* also occurred in sarcomas (sarcoma of the femur, melanotic form).

22. White, C. P.: On the Occurrence of Crystals in Tumours, *J. Path. & Bact.* **13:3**, 1909.

23. Roffo, A. H.: The Cholesterol Ratio in Tumors, *Prensa méd. argent.* **11**: 1060 (April) 1925; **11:28**, 1924.

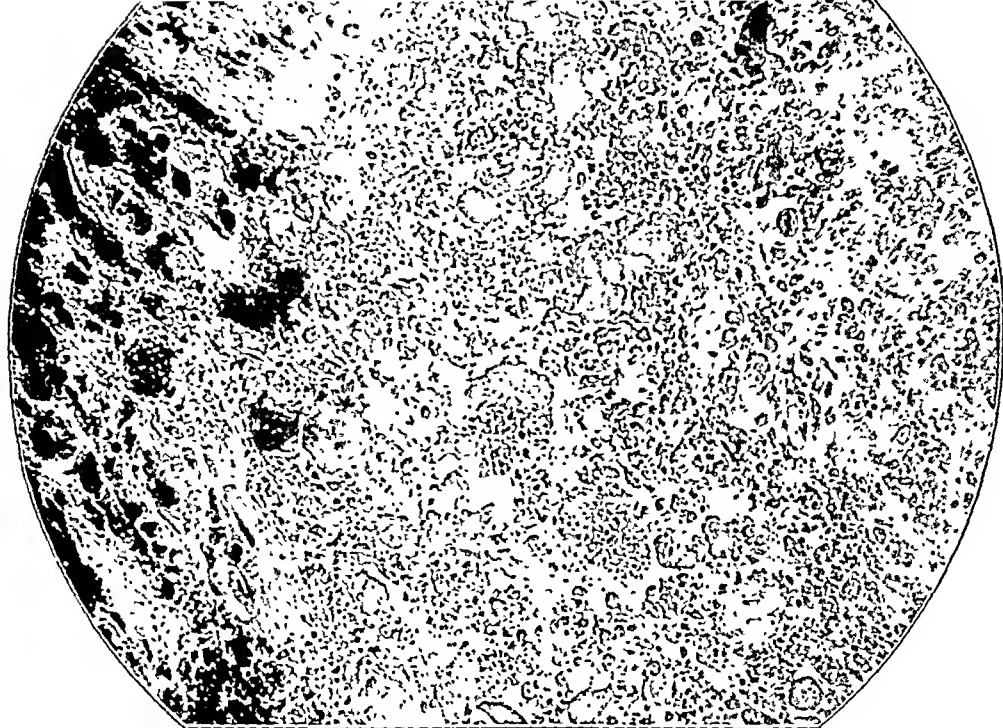


Fig. 12.—Field 2: mixed (arc) light; green and yellow filter. This gives a good general perspective of the entire composition of the section.

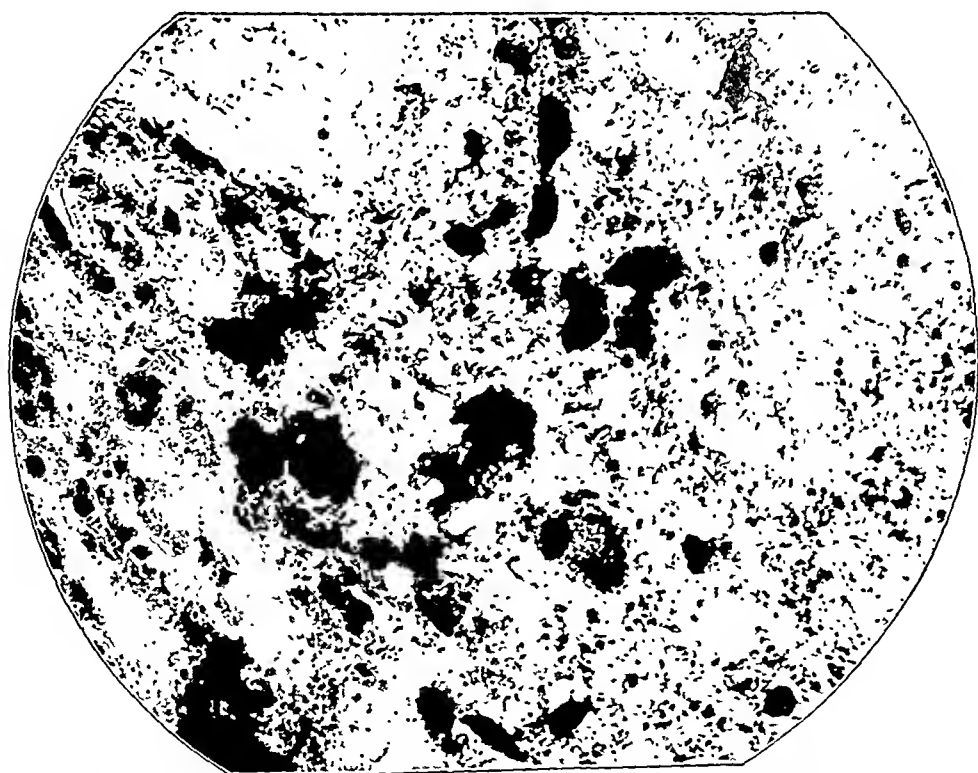


Fig. 13.—Field 2: mixed (arc) light; blue filter. Only the neutral fats stained with sudan III are registered.

White's studies thus indicated that polarized light was not available for quantitative chemical analysis of the different fatty substances; only one of the five crystals that he classified was pure, and probably the amorphous masses were likewise mixtures. Thus only the isotropic substances could be identified with certainty as a group of lipids totally apart in any one respect from another group. Unfortunately the contrasting group of anisotropic particles (containing isotropic substances also) do not justify comparison because they are so indefinitely composed, quantitatively; their indefiniteness disturbs any attempt at mathematical comparison.

Even in 1909 White realized the rôle which the factor of "mixture" played in maintaining lipids in solution:

Apparently these substances help to keep one another mutually in solution in the body fluids, from which they may, under certain conditions, separate in the crystalline form. It has long been known that lecithin forms a fine emulsion or a colloidal solution in water, and it does this because of the cholesterin which it contains. When freed from cholesterin it no longer becomes emulsified with water. Similarly, cholesterin mixed with fatty acids forms a fine emulsion with water, especially if a trace of alkali be present. These emulsions or colloidal solutions are unstable, being easily precipitated by the addition of acids or salts.

This statement antedates some of the pronouncements of Schaaf² by twenty years.

As to the xanthosarcoma reported here, information was especially desired concerning the lipid partition of cells in the more central parts of the tumor as compared with the partition of those at the periphery. It was conceivable, assuming that the peripheral parts were growing more actively than the central ones, that there would be an absorption of neutral fats from the central parts of the tumor (neutral fats and soaps being more readily absorbed and removed) and that the residue of cholesterol would be greater in the center than at the periphery. It was thought that an approximation could be obtained on the basis of singly refractive and doubly refractive substances, together with the behavior of the substances toward staining with sudan III. Accordingly, emulsions were tested by these methods, as follows:

Samples of tissue were taken from ten portions of the tumor: (1) interosseous fibrous tissue, (2) the most central parts of the tumor, (3) the summit of the fungus growth (superficially ulcerated), (4) the fibrous capsule, (5) the central part of the tumor, (6) aerolar fat, (7) muscle, (8 and 9) the peripheral advancing part of the tumor (two portions) and (10) a portion at the junction of the fibrous center and the definitely xanthomatous part. The latter block of tissue was selected to represent as closely as possible the zone of transition between the more fibrous portions in the interosseous membrane and the more definitely xanthomatous parts peripherally. The positions of the various portions are indicated in figure 2.

The samples of tissue from the different parts were ground up, emulsified in water and examined after being stained with sudan III and by polarized light. Other portions of the emulsion were extracted in hot alcohol, filtered, evaporated to small volume and similarly examined. The latter procedure was necessary to avoid the intermixture of collagenous and other fragments which were also doubly refractive and which in their finely subdivided state could be distinguished from fatty substances with difficulty.

Anisotropic substances in significant quantities occurred only at one position, i. e., at the summit of the fungus-like growth, where superficial ulceration had taken place. Elsewhere the quantities of anisotropic substances were negligible. In short, almost all of the fatty substances were neutral fats. It was surprising that the normal areolar fat contained as much anisotropic material as the tumor, even in the ulcerated, superficial part just mentioned. Thus the composition of the tumor was found to be comparatively uniform as between isotropic and anisotropic substances; it was estimated that less than 1 per cent of the lipids were doubly refractive.

Cholesterosis of the General Body Fat.—That hypercholesterosis, as seen in endothelium and in white fibrous tissue cells of xanthoma, could also occur in other, normal tissues which contain fat (fatty areolar tissue) was suggested by White's work in which he showed that the fatty globules and crystals were seldom chemically pure neutral fat or chemically pure cholesterol, but mixtures. This held good even for fat in crystalline form. While repeated crystallization makes for purity of a chemical substance, the converse is not true. A crystalline form does not guarantee chemical purity.

After White's conclusions it was only a short step to the question whether, under certain conditions of hypercholesteremia, the cholesterol and other lipids could pass into solution in normal fatty areolar tissue. For example, certain authors have reported that fatty crystals occur in otherwise normal areolar tissue, as Gray²⁴ found in his work on sclerema neonatorum and Proescher and Meredith²⁵ in their study of myxolipoma.

As to the case reported here, normal areolar fat at a distance of 2 or 3 mm. from the xanthosarcoma contained numerous anisotropic crystals. However, this fact could not be invoked as evidence of widespread systemic cholesterosis of fat, because diffusion could account for it, i. e., local absorption from a nearby focus of such extreme

24. Gray, A. M. H.: Sclerema Neonatorum, Arch. Dermat. & Syph. 14:635 (Dec.) 1926.

25. Proescher, F., and Meredith, E. W.: Multiple Myxo-Cholestro-Lipomata, Surg., Gynec. & Obst. 9:578, 1909.

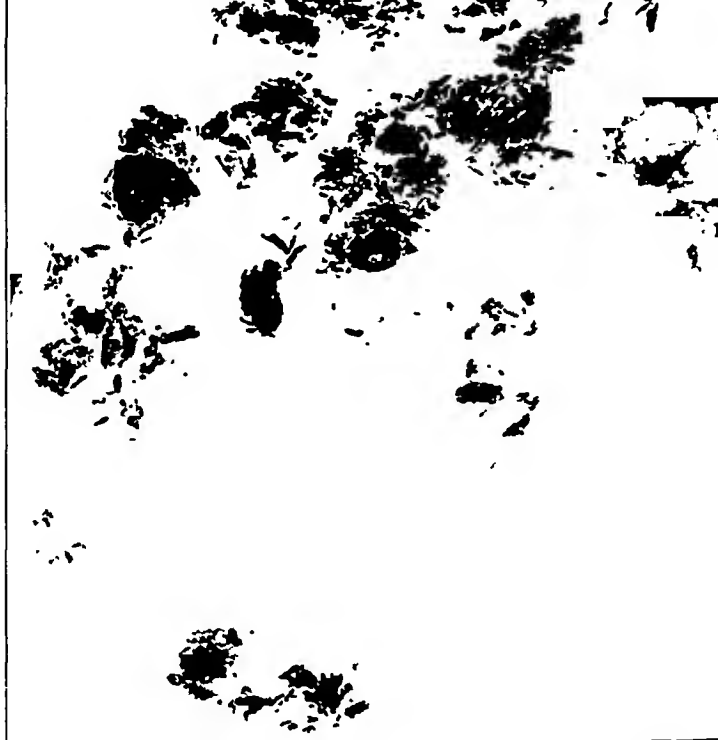


Fig. 14.—Field 1: polarized light; green and yellow filter.

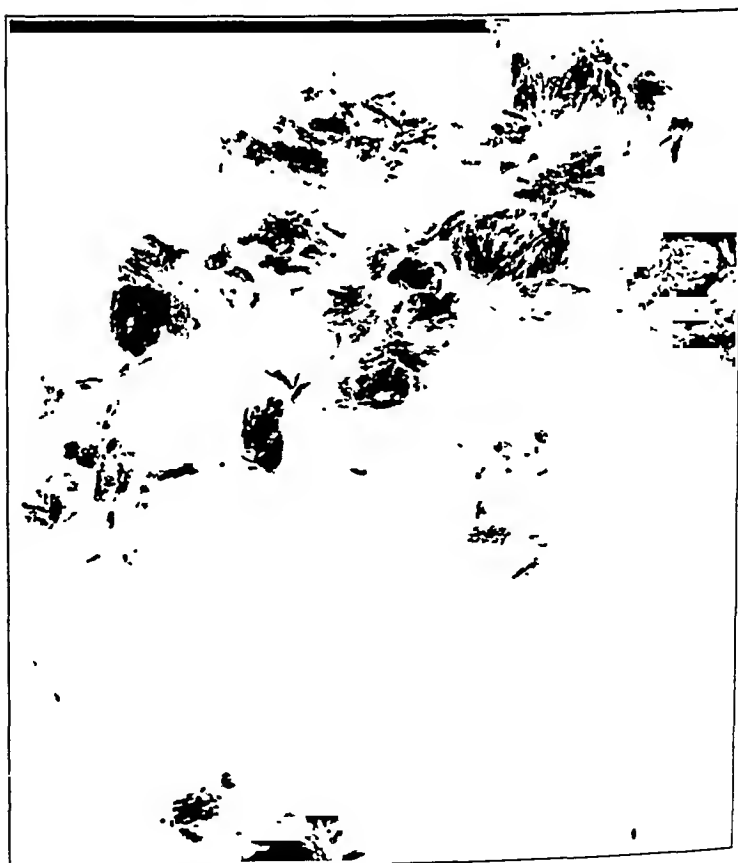


Fig. 15.—Field 1: polarized light; blue filter.

fatty change. Fat 2 or 3 cm. away contained even fewer anisotropic crystals. Fat from the palm showed negligible quantities of this substance.

Thus it appears that even in tissue preserved for several years in formaldehyde, anisotropic fat did not occur in the general areolar fatty tissue. Small quantities diffused outward for short distances from the xanthosarcoma.

XANTHOMATOSIS IN TUMORS OF THE CONNECTIVE TISSUES

Sufficient has been said already about xanthomatous examples of the commonplace fibromas—fibrosarcomas of tendon sheaths—based on the compilations of Tourneaux, Krogius, Harbitz and Bloodgood. The accompanying table is designed mainly to indicate the range of other tumors which may be affected by xanthomatous changes.

I wish to call attention to what has been stated already about the basic pathologic process of foam cell tumors, i. e., that there are probably good reasons for regarding some of the tumors in the succeeding table as composed of cells which are "fundamentally, metabolically" lipoidal in nature, such as the xanthomas of tendon sheaths. In the case of tumors having an endothelial basis, such as hemangiomas and lymphangiomas, the presence of cholesterol may well be a secondary, more or less accidental addition. Lubarsch²⁶ advocated a special nomenclature to apply to these, recommending that they be called "fibroma xanthomatousum," "lymphangio-xanthomatousum," etc. That is, the designation "xantho-" would be used to indicate that the intrinsic cells of such tumors were not fundamentally lipoidal any more than *Hersfellerszellen* are fundamentally pigmentary.

It is appreciated that some of the tumors listed may overlap biologically, as the nomenclature of one author may not coincide with that of another. The "granulation tissue" tumor of Garrett, for example, may well be chronically inflammatory and not at all neoplastic. I think that this is true in the case reported by Lebedew. However, the diagnoses of the different authors have been taken at face value, and it has been left to the reader to appraise the interrelationship of the different lesions listed.

The table gives a general perspective of the range of tumors or quasitumors which may be affected by xanthomatous change. Further insight may be gained by the few comments which follow.

Granulation Tissue Tumors (Garrett¹).—It must be conceded at the outset that these were not neoplasms. In a symposium on xanthomas, opened by Bloodgood,¹⁵ two of his pupils (Garrett¹ and David T.

26. Lubarsch, O.: Generalisierte Xanthomatose bei Diabetes. Deutsche med. Wchnschr. 44:484, 1918.

erythrocytes; no data were submitted bearing on this point. Therefore, these seventeen "tumors" resolve themselves in principle into peculiar pigmented scars which may or may not have exhibited foam cells of the order of those seen in arterial atheroma.

The report of Lebedew's case in which numerous tumor-like masses of granulation tissue occurred in the mouth and on the skin has been abstracted in full in a previous section of this paper.

Neurofibroma.—I refer here to a particular example, i. e., tumor of the cerebellopontile angle (tumor of the acoustic nerve), described in full by Henschen.²⁸ Details may be found elsewhere.² Some of these tumors contain so much cholesterol that they have received the name cholesteatoma. In one case they were found associated with xanthomas of the skin (Delore²⁹).

Myxolipoma.—This was an extraordinary neoplasm occupying almost the entire abdominal cavity, associated with similar tumors in the calf, groin, breast, pleura and lung and on the surface of the liver. Microscopically it consisted of stellate cells together with round cells which contained fat. Doubly refractive crystals were found in the fatty materials. It was probably a pluricentric myxolipoma originating in subserous and subcutaneous fat. The intermixture of doubly refractive substance was small; a determination of the blood cholesterol was not made, nor was "normal" fat from remote parts of the body tested. It would be interesting to know whether the anisotropic fat observed in this tumor was present simply as a part of the general lipoidal storage processes in the normal and otherwise fatty parts of the body.

Capillary Angioma.—One such tumor, in a joint, was encountered by Garrett in the studies already mentioned. Pigment was associated with the foam cells.

Hemangioma Cavernosum.—This was a tumor the size of a nut in the muscular tunic of the ileum, exhibiting yellowish white points which were xanthomatous histologically. The fat occurred in the hyperplastic endothelium of the blood spaces. Incidentally, the patient had cancer of the gallbladder, suggesting strongly that hypercholesteremia was present. Petri³⁰ concluded that almost all kinds of cells, in addition to fixed connective tissue cells, can probably become xanthic.

Lymphangioma.—Kirch³¹ saw two polycystic lymphangiomas of the knee, each about the size of an egg. The endothelial linings of the

28. Henschen, F.: Histology and Pathogenesis of Tumors of the Cerebellopontine Angle, Arch. f. Psychiat. **56**:20, 1915.

29. Delore, cited by Henschen.²⁸

30. Petri, E.: Zur Kenntnis der xanthomatösen Gewebsumwandlung: Haemangioma xanthomatosum, Centralbl. f. allg. Path. u. path. Anat. **34**:1, 1923.

31. Kirch, E.: Xanthomatous Tumors, Klin. Wchnschr. **3**:1425, 1924.

spaces contained the fat, which was responsible for the yellow color; hence fibrosis is not a *sine qua non* for xanthoma. Kirch's communication may be regarded as a model in the investigation of xanthomatous tumors; he examined the blood cholesterol values in eight cases, with the following results:

	Cholesterol, Mg. per 100 Cc.
Polycystic lymphangioma	302 to 313
Polycystic lymphangioma	256.7
Endothelioma of the dura.....	481
Fibrosarcoma of the thigh.....	190 to 173
Fibrosarcoma of the leg.....	255
Sarcoma of the arm.....	450
Fibrosarcoma of the ankle.....	179 to 284
Giant cell granuloma of the finger.....	187

Furthermore, he found that even after the surgical excision of a tumor the blood cholesterol remained high; i. e., the tumor was not acting as a depot for the fabrication of the cholesterol. Kirch's description of the pathologic process of xanthomatosis is a masterpiece; among other things he stated that "neoplasms of most diversified localization and kind can become xanthomatous, even epithelial ones."

Fibrohemangioma.—Garrett studied the impressive number of seventy-six fibrohemangiomas, of which nineteen were xanthomatous. I think that hemangiomas, of all tumors, need least association with general hypercholesteremia to explain their xanthomatosis. With red blood cells so rich in cholesterol and with such opportunities for stasis and disintegration as occur in hemangiomas, I believe that there is a likelihood of local absorption of cholesterol, just as cholesterol crystals frequently appear around areas of hemorrhage in tumors. That is, xanthohemangiomas are readily explained on the basis of local xanthomas (Stewart³²); general hypercholesteremia need not be invoked.

Fibroleiomyoma (Wessen³³).—This was a tumor the size of a grapefruit, occurring intrathoracically, or to be exact, retropleurally. Smooth muscle fibers occurred throughout the tumor and under the capsule. Wessen believed that the tumor had its origin in embryonal derivations, possibly of the esophagus.

Endothelioma.—This lesion, occurring in the dura, was one of the eight xanthomatous tumors described by Kirch. The dura is a rather common seat of xanthomatous change. It is involved in diabetic

32. Stewart, M. J.: On the Cellular Reactions Induced by Local Deposits of Cholesterol in the Tissues, *J. Path. & Bact.* 19:305, 1915.

33. Wessen, N.: Xanthomatous Intrathoracic Tumor, *Acta chir. Scandinav.* 53:621 (June) 1921.

xanthoma; it was noted by Pinkus and Pick³⁴ in a case of generalized xanthomatosis; it is commonly involved in Christian's disease (one of the juvenile forms of generalized xanthomatosis) and has been studied by neurologists in connection with tumors of the acoustic nerve. Under these circumstances it is doubtful that a xanthomatous "tumor" of the dura should be regarded as truly neoplastic, for by the time fibrous tissue cells become swollen and otherwise distorted by xanthomatous infiltration it is difficult in most cases to identify the mother cell of the tumor as endothelial or even neoplastic. Many or most dural "xantho-endotheliomas" are doubtless simply xanthomatous masses of hyperplastic endothelium or fibrous tissue.

Lymphangio-Endothelioma.—Carol Smith³⁵ worked in the laboratory of Pick in Berlin, the center of studies of xanthoma in Europe. He analyzed four cases which had accumulated in Pick's laboratory; of the two lymphangio-endotheliomas included, one involved the tongue and the other the vulva.

Sarcoma.—The various kinds of sarcomas noted in the table, i. e., giant cell and polymorphous cell sarcoma and fibrosarcoma, as well as the fibromas which may be regarded as having undergone xanthomatous change, have been discussed sufficiently in the early portion of this paper. It will be recalled that under critical analysis few were found to exhibit true metastases, whereas regional metastasis to the lymph nodes and local recurrence were noted frequently.

Gast and Zurhelle³⁶ deserve special mention, however, because in the study of their case of xanthosarcoma of the thigh they analyzed the composition of the fat, finding equal parts of neutral fat and cholesterol. Most cells contained only one kind of fat, while a few contained both kinds. They mentioned hypercholesteremia, although they did not inquire about its presence in their patient. They stated, however, that in the future an antecedent hypercholesteremia must be considered in xanthoma.

PATHOLOGY

Two phases are concerned, the sarcomatous and the xanthomatous. Obviously the general pathologic process of sarcoma will not be considered here. It is sufficient to say that whether the tumor in the case reported here was fibrosarcoma at the beginning or not, at operation it was a mixed spindle cell and round cell tumor.

34. Pinkus, F., and Pick, L.: Xanthoma and Foam Cell Tumors, with Report of a Case of Generalized Xanthoma Tuberosum, *Dermat. Ztschr.* **15**:706, 1908.

35. Smith, C.: Histology and Nature of the So-Called Foam Cell Tumors, *Surg., Gynec. & Obst.* **14**:551, 1912.

36. Gast, E., and Zurhelle, E.: Xanthosarcoma of Thigh, *Berl. klin. Wchnschr.* **55**:930, 1918.

Metastasis.—A further word must be said on the subject of metastasis in the case reported. The reports in the literature of metastasis of xanthosarcomas have already been reviewed, and only one authentic instance was found. Furthermore, the congener fibrosarcoma metastasizes only exceptionally. In this light judgment must be carefully balanced concerning the facial lesion in my patient. Thus, according to the rule for metastasis of sarcoma, the organs involved should be the lungs, liver and other viscera liable to a rich hematogenous distribution. The deep tissues of the face certainly do not fall in this category.

Fortunately, there is an alternative solution. At this point the reflections of Proescher and Meredith³⁷ apply because they also reported tumors (multiple myxocholesterolipomas) the anatomic location of which was so inconsistent with a hematogenous distribution that they decided in favor of multiple primary tumors. This can apply also to fibrosarcoma and the xanthosarcoma in my case, if the hypothesis already proposed can be permitted, that the xanthosarcoma was basically a fibrosarcoma, with a superadded xanthosis. For example, there are several analogous reports in the literature of so-called metastasis of the fibrosarcoma of the extremities to the dura, which are singularly analogous in principle to the condition in my case; thus my case does not stand alone in respect to this apparent inconsistency in metastasis. Rather, it is in order to think as Proescher and Meredith did, namely, that a pluricentric formation of tumors is concerned in fibrosarcoma and in xanthosarcoma also; as in multiple myeloma, there may be something consistent (in the direction of development of tumors) in the kind of tissue in which the tumor originates, even though it is located in diverse parts of the body.

There was a further consideration in my case that bore on the situation, namely, the history of a possible origin of the facial lesion around or in the socket of a tooth. In dense fibrous tissue like that of the periosteum or the gingivae sequestrums may have maintained a continuous focus of irritation, provoking at least the formation of granulation tissue. Whether this mounted to the proportions of fibrosarcoma or not, the known xanthomatous propensities of the patient assured an opportunity for the development of at least a xanthoma at this site. A full description of scar xanthoma, including locations at the roots of the teeth in Christian's disease, has been given elsewhere.³⁷

37. Weidman, F. D., and Boston, L. N.: Generalized Xanthoma Tuberosum with Xanthomatous Changes in Fresh Scars of an Intercurrent Zoster: Adenocarcinoma of The Ampulla of Vater at Necropsy, *Arch. Int. Med.* **59**:793 (May) 1937. Weidman, F. D., and Stokes, J.: Extensive Xanthoma Tuberosum in Childhood Due to Infectious Cirrhosis of the Liver, *Am. J. Dis. Child.* **53**:1230 (May) 1937.

There is thus an accumulation of disconnected angles of the xanthoma-fibroma-sarcoma situation that admit the facial lesion on other than a metastatic basis; there is no heresy in regarding it as a focus metastatically independent of the lesions on the arm and skin.

Xanthogenesis.—Tumors may exhibit the xanthomatous phase in at least two and possibly three forms: First, the phase may be exhibited as an essentially local phenomenon, i. e., as an end-result of simple degenerative and necrotic changes such as can occur in large morbid masses in general. Second, the rôle of an abnormal general fat metabolism, whether hypercholesteremia accompanies it or not, must be taken into account as a force operating on (neoplastic) cells which are admittedly unbalanced metabolically and yet have a threshold high enough to endure ordinary normal fat conditions in the environment. Here the tumor, in becoming xanthomatous, would simply be sharing in and succumbing to the general lipoidosis. Finally, a third form of xanthomatous change can be assumed as the expression of an inherent property of the particular neoplastic cell concerned—a matter of fundamental cellular metabolism peculiar to it, which would endow it with the same properties as those peculiar to a lipoma, except in the differing composition of its fats.

Twenty years ago Carol Smith³⁵ outlined the pathologic process of xanthoma. He noted that cholesterol appears in tumor cells (and only in those of the connective tissue series) under the following circumstances: (1) when the tumor cells originate in an organ which normally contains cholesterol, i. e., the Grawitz tumor; (2) when the cholesterol is set free in the tumor as a product of degeneration; (3) when the cells assume special metabolic rôles (in the direction of cholesterol). This new property persists in the neoplastic cells. These subdivisions will be considered further. Some of the mechanisms by which xanthomatous changes are produced in tumors are as follows:

Local Xanthomatous Changes.—Among these Stewart³² included dermoid cyst, cholesteatoma, testicular teratoma and epithelioma. As to the presence of cholesterol, he cited White: "In tumors generally, and especially in carcinomas . . . apart from any necrotic changes." In all of the lesions lipids are liberated locally, independent of the neoplastic cell itself; thereafter, in the presence of fluids surcharged with lipids the neoplastic cells assume xanthomatous features (absorption of cholesterol?).

Globus³⁸ reported a "teratoid cyst of the hypophysis;" his excellent illustrations leave no doubt of at least some xanthomatous intermixture, although he referred the fatty cells to incomplete development of cells of the sebaceous glands. This was the interpretation that Kaposi, many

38. Globus, J. H.: Teratoid Cyst of the Hypophysis, Arch. Neurol. & Psychiat. 9:417 (April) 1923.

years ago, placed on xanthomas. Pituitary xanthomas have been reported a number of times (as in Christian's disease) and may not be "local." However, in such a richly lipid environment they may properly suggest this origin. Incidentally, Oudendal³⁹ observed doubly refractive crystals in a sarcoma of the thyroid; he ascribed them to repeated hemorrhages, from which cholesterol crystals developed. He also called attention to the protein Charcot-Leyden crystals, which might constitute sources of error in studies of local xanthomatous residua.

Local degenerative and necrotic changes in a large morbid mass such as a neoplasm can account for some xanthomatous changes which have been reported in tumors. In such a case there is a focus of fatty materials, including such various substances as neutral fats, soap, cholesterol and phosphatides. The imbibition or phagocytosis of these substances by connective tissue and other cells gives rise to the well known foam or xanthoma cells, but, in addition, the fatty substances appear intercellularly. The proportion of the different fats varies in different lesions. In my opinion neutral fats and soaps should be absorbed more readily than cholesterol when free in tissue spaces, and it is to be expected that the proportion of these substances varies largely in a given lesion from time to time, depending on the rate of absorption and particularly on the age of the lesion.

There is no reason why secondary changes of the same order should not occur in lesions which, like xanthoma tuberosum and xanthosarcoma, are conceivably xanthomatous from the beginning, i. e., lesions in which the question of the proportion of the lipids is fundamental and important for a knowledge of their pathologic processes, especially in attempting to reconcile the cellular fatty conditions with those of the blood. In such cases the valid chemical data on the fats, i. e., those representative of the basic process, would be obtained only from the *early* lesions. Therefore, care should be exercised in selecting the materials designed for chemical analysis when it is proposed that the figures obtained for lesions are to be compared or reconciled with those for circulating blood fat or for similar factors in the disordered fatty state.¹⁹

Essential or Intrinsic Xanthomatosis.—The cell comprising a tumor of a tendon sheath probably should be regarded as a special kind of xanthoma cell, although morphologically it cannot be distinguished from other foam cells (diabetic xanthoma). What special place these cells merit in the classification of xanthomas depends on their fundamentally different genesis. Thus, the cells from which such tumors spring have the inherent, specific property of elaborating cholesterol just as the cells of the adrenal glands have, whereas the other members of the xanthoma

39. Oudendal, A. J. F.: Crystals and Pigments in Living Tissues, Mededeel. v d. burgerl. geneesk. dienst in Nederl.-Indie, 1925, p. 1.

group are supposed to take cholesterol more or less passively into their cell substance; that is, these cells of the tendon sheaths are blastomatically lipoidal. This concept, original with Sick,⁴⁰ was disputed by Pick, who preferred to look on all xanthomas as comprised of nonspecific cells (hemangiomas, fibromas, granulation tissue); these cells differed from ordinary tumor cells only in that, more or less secondarily, the lipid substances had become infiltrated. It is assumed that Pick has now departed from his original position and recognizes the concept of the "foam cell" tumor as his pupil, Petri,⁴¹ subsequently described a xanthocarcinoma of the stomach. The tumor cell in Petri's case was (in both the primary and secondary lesions) that of a gastric adenocarcinoma; there were no degenerative changes to permit the interpretation that it was a secondary change in connection with local hypercholesterosis.

Incidentally, in Pick's laboratory careful study was made of the nature of the fat concerned, with the result that doubly refracting substances were not found in this xanthocarcinoma cell; neutral fats were exclusively concerned. I feel, however, that a further statement of Petri—which doubtless is supported by Pick—namely, that the foam cell tumor can contain only neutral fat, is going too far. That it was true in Petri's case of xanthocarcinoma is conceded, but from the observation of a solitary case this property should not be postulated as a constant one for all foam cell tumors. Thus, before reading Sick's paper, I had come independently to the opinion that the tumor in my case belonged in the foam cell group, i. e., that it was not a "symptomatic" or a "local" xanthoma. Contrary to Petri's contention, in this tumor there were demonstrable, although scanty, quantities of doubly refractive substances.

In my opinion the concept of the foam cell tumor is mostly academic from the standpoint of the genesis or basal metabolism of the cell concerned. "Foam cells" in the sense of Sick cannot be differentiated morphologically from xanthoma cells. It is only by estimating the derivation of the cell concerned—whether from the adrenal, prostate, or some other gland—and perhaps by the exclusion of certain forms, such as local and symptomatic xanthomas, that the diagnosis of foam cell tumor can be made. Only when it is finally known just how the fat has developed in a given case of xanthoma will it be possible to make rational subdivisions and arrange a logical classification.

40. Sick: Ueber Xanthoma und Schaumzellentumoren, mit Bericht eines Falles von generalisierten Xanthoma tuberosum (Discussion), *Dermat. Ztschr.* **15**:710, 1908. "Foam cell tumor" was Sick's designation; this is obviously inappropriate, because "foam cell" also fits xanthomas other than fundamentally, metabolically lipid ones.

41. Petri, E.: Ein Beitrag zur Kenntnis der sogenannten Schaumzelltumoren, *Frankfurt. Ztschr. f. Path.* **27**:507, 1922.

Furthermore, it is only with a knowledge of all the involved considerations concerning fatty infiltration and fatty degeneration (applying to neutral fats only, presumably), as outlined by Adami,⁴² that the full and proper perspective of the situation can be arrived at. The involved considerations in connection with these subjects also apply to cholesterol and other lipids; the cellular biology of xanthomatous change can never be approached and definitely recorded until it is examined in the same light as "fatty infiltration" and "fatty degeneration."

Summary.—A comparison of the data on benign xanthoma tuberosum, taken as a standard, with those on the xanthosarcoma reported here revealed nothing (particularly morphologically) which indicated any differences in the essentially xanthomatous processes, barring the embryonal cytology to be expected in any sarcoma. The xanthoma cells in my case resembled equally those of xanthoma tuberosum and of Christian's disease. The normal or nearly normal blood cholesterol value for my patient is not significant in any particular direction; it has been noted in numerous cases of non-neoplastic xanthoma.⁵

For this particular case of xanthosarcoma the way is theoretically open to explain the xanthomatous phases in two of the three ways just mentioned. First, this lesion may have been fundamentally a fibrosarcoma; in the presence of a high fat value for the blood the tumor cells absorbed abnormal quantities and became infiltrated by fat. This presupposes a period of hypercholesteremia, which this patient did not have when tested, but probably experienced at other times (there was a clinical history of pregnancy). Or second, the tumor cell may have been faulty in respect to its handling of fats from the beginning and may have been xanthosarcomatous independently of fatty conditions (foam cell tumor of Sick).

Unfortunately, the blood cholesterol values are not definite enough to assist in deciding between the two possibilities. Certainly the factor of degeneration and necrosis, with the production of local xanthomatous depots (as illustrated in old residual abscesses), was not operative in this xanthosarcoma; numerous blocks of tissue were searched microscopically, and there was nowhere a frank degeneration, much less necrosis.

There are no proponents of a theory that the tumors are the source of hypercholesteremia, if this is present. It is doubtful that even such a large depot of cholesterol as this sarcoma could account for the scant increase in the blood cholesterol value by a discharge into the circulating blood. Kirch found that the operative removal of xanthic tumors was not followed by the disappearance of hypercholesteremia.

42. Adami, J. G.: *Principles of Pathology*, ed. 2, Philadelphia, Lea & Febiger, 1910, vol. 1, p. 20.

For fibromas and fibrosarcomas of tendon sheaths in particular it is natural to wonder what connection their specialized lining endothelial cells, involving as they do a quasisecretion, can have with a cell like that of xanthoma and xanthosarcoma which accumulates cholesterol. Normal synovial fluid contains from 0.06 to 0.07 parts per thousand of fat (Hammarsten⁴³). It is sometimes milky and contains degenerating cells, i. e., there are possibilities of the source of cholesterol being immediately at hand. Lubarsch²⁶ and others independently saw lymphatic stasis as a predisposing factor in xanthomatous deposits; the tendon sheaths, being so highly developed, involve extensively the circulation of the lymph. In the presence of a neoplastic swelling of tendon sheath cells, stasis of the fluid of the tendon sheath is likely to follow and to accentuate whatever xanthomatous tendencies are already established. It is agreed that stasis alone cannot induce xanthomatosis.

While the pathologic process of xanthosarcoma is, thus, definite in many respects, particularly as to the morbid anatomy, it becomes most unsatisfactory when the precise etiology is approached. Furthermore, the prospect of enlightenment is remote in view of the infrequency of cases with which to work.

SUMMARY AND CONCLUSIONS

A fatal case of xanthosarcoma is reported which is almost unique on account of nodules in the oral mucosa and deep tissues of the cheek; while there are some observations which point to metastasis from the lesion on the forearm, it is more likely that the two foci developed independently as the result of separate trauma or as "tumors of multiple origin." Whether metastatic or pluricentric, multiple xanthosarcomas must be given a guarded prognosis; multiple tumors, as in my patient, can acquire a practical prognostic significance comparable to that of metastatic tumors.

Reports of cases of xanthomatous tumors collected from the literature are listed; the growths in these cases include fibroma, neurofibroma, myxolipoma, angioma, endothelioma and sarcoma. Even carcinomas may be xanthomatous.²

A photographic method, employing polarized light and different filters, is described for more accurately distinguishing quantitatively between anisotropic and isotropic fatty substances.

The pathologic process in xanthic tumors of the connective tissue is discussed fully. I believe, with Sick, that the cells of xanthomatous tumors of the tendon sheaths are, like adrenal and some other cells (prostate, corpus luteum), fundamentally metabolically "constituted" in

43. Hammarsten, O., and Hedin S. G.: *Text-Book of Physiological Chemistry* ed. 7, New York, Wiley & Sons, 1915, p. 362.

the direction of production of lipids. Perhaps special function and the composition of the synovial fluid (lubrication, degenerated cells) point in this direction for xanthomas of tendon sheaths.

In general, there are numerous analogies between fibrosarcoma and xanthosarcoma, in the relation to trauma, the origin in tendon sheaths and other fibrous structures, slow growth and local malignancy. Distant metastasis of xanthosarcomas appears to be unknown, contrary to recent reports in the literature.

Extensive yellow coloration of sarcomas, particularly of the extremities, may be due (1) to necrosis or pigmentation or (2) to xanthomatous change. Since necrosis and pigmentation are retrogressive processes common to a great variety of neoplasms and do not connote a peculiar and important metabolic addition to the situation as xanthomatosis does, it is recommended that clinical expedience be set aside, and that the term xanthosarcoma be reserved for those cases in which true xanthomatous changes are associated, as evidenced histologically by the presence of xanthoma cells.

While they probably have no bearing on prognosis and treatment, the significance of xanthomatous processes observed in sarcomas should not be forgotten in relation to lipid metabolism in its widest aspect, including cholesterol and its esters. While my patient did not have hypercholesteremia, and the lesion contained comparatively little lipoidal substance, the way is still open to identify some particular order of general systemic fatty disturbance in other cases of xanthoma and (or) xanthosarcoma. It is urged that this be inquired into in future cases of xanthoma and xanthosarcoma. Such inquiries would answer the question whether one is overlooking a general fatty dyscrasia in the xanthomatous patient, which is far more important to his well-being than the tumor which, more or less incidentally, is signaling the information.

Histologic sections are deposited in the Laboratory of Dermatological Research, University of Pennsylvania (D. R. 2275), and at the Army Medical Museum, Washington, D. C. (36477).

INHIBITION OF THE BLADDER

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AND

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ST. LOUIS

The physiologic basis of many varieties of dysfunction of the bladder is as yet ill understood. Patients present themselves with frequency, urgency or difficulty in urinating for which no adequate explanation is found in the urinary tract. Although it is generally recognized that a lesion of the central nervous system, of the peripheral nerve supply or of the musculature of the bladder can produce dysfunction, the actual cause of symptoms in many patients is frequently overlooked.

In interpreting these symptoms assistance is obtained by studying the activity of the bladder and the sensations experienced by the patient during filling. By using a cystometer with a constant recording mechanism, a graphic representation of the reaction of the bladder to filling is made, and the points at which sensations are experienced can be plotted on the tracing. However, it is well to keep certain effects in mind in interpreting the curves. It is generally recognized that the pressure attained at any volume in the normal bladder will depend on the rate of introduction and also on the temperature and type of fluid used. Temperatures of either extreme and too rapid filling are to be avoided. It is less well recognized, however, that psychologic effects, particularly those resulting in inhibition, may produce curves from a normal bladder which simulate gross pathologic conditions. To obtain a fair idea of the effect of such influences, which operate to a greater or a lesser degree in the making of all cystometrograms, at least two curves should always be made.

It is important also to distinguish between the true contraction of the detrusor urinal muscle and a rise of pressure due to abdominal straining. If the rise is due to the latter cause, it can be sustained only while the breath is held, and when straining is stopped the writing point immediately falls back to the starting level. The contraction of the detrusor muscle, on the other hand, continues in spite of normal breath-

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ing. and even if the reaction is controlled by voluntary inhibition, the writing point descends slowly and in a series of steps.

The observations submitted here are the results of a study of the inhibitory effects on the bladder in certain patients with dysuria. The cystometer, introduced by one of us (Dr. Rose) in 1926, was employed, and the technic previously described was used.^{1a}

CYSTOMETROGRAPHIC DATA AND CLINICAL APPLICATION

Curve *A* in chart 1 represents the cystometrogram of a normal subject. The pressure was adapted to the volume smoothly, and the tension rose more rapidly as the limiting volume was reached (indicated by an asterisk), terminating in a spontaneous expulsive reaction. Here the bladder reacted to stretch by a simultaneous coordinate contraction, producing a smooth curve.

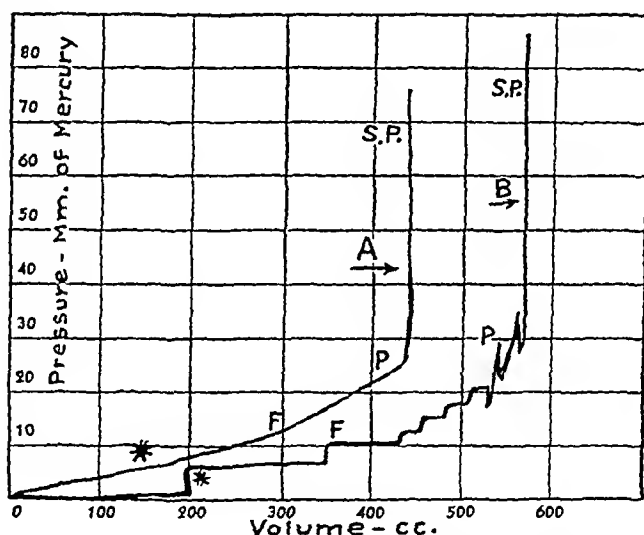


Chart 1.—Cystometrograms of a normal subject. In this and the following charts the asterisk indicates the first desire to void; *F*, fulness; *P*, pain, and *SP* severe pain.

Curve *B* in chart 1 is another tracing made at the same examination. The subject was asked to relax the bladder as much as possible and to try not to void. The curve is flat for 200 cc., at which point there was an abrupt rise of 6 mm. of mercury, which was associated with a slight sensation in the bladder. This rise was immediately inhibited, and filling continued on a plateau of pressure for about 150 cc., when a second rise occurred. This process was repeated with shorter plateaux as the distention proceeded, producing a "step" effect, and it will be noticed that two diphasic waves occurred in the early phase of the emptying contraction of the bladder. In this patient inhibition had the effect of permitting a

1. (a) Rose, D. K.: Determination of Bladder Pressure with the Cystometer: A New Principle in Diagnosis, *J. A. M. A.* 88:151 (Jan. 15) 1927; Changes in the Wall of the Bladder Secondary to Prostatic Hypertrophy, *Arch. Surg.* 25:783 (Oct.) 1932.

greater amount of stretch to take place without an increase in the resistance of the wall of the bladder, but this amount grew progressively less with increasing volume and the resulting tendency for inhibition to be overcome.

These two curves, that produced without attempt at inhibition (*A*) and that produced with an attempt at inhibition (*B*), demonstrate the variability in normal curves as influenced by inhibition. Notably curve *B* should be higher and shorter than curve *A*, but it is lower and longer as a result of inhibition. It is a fact that in the neurogenic bladder of the diminished sensation type the normal relationship is reversed just as is shown in chart 1, often so much that it is unwise to overdistend such a bladder. If the cause of the reversal is inhibition, it is suggested

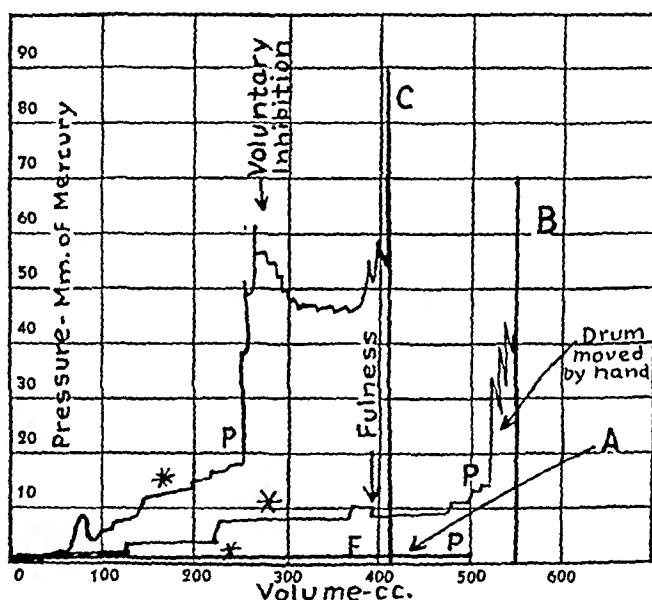


Chart 2.—Cystometrograms of an introspective subject.

at the time by the action of the patient and can be checked by still another cystometrogram, as the repeated filling and emptying of the bladder of normal innervation will decrease capacity and increase intracystic pressure.

Three tracings (chart 2) were made at the same examination of an introspective person who, in addition to being unduly fearful, experienced considerable pain from the catheter due to posterior urethritis. Curve *A* is entirely flat for 500 cc., with no reaction of the detrusor muscle; yet filling was stopped on account of pain caused by overdistention. When curve *B* was made the patient was less frightened, and the pain in the urethra had subsided, probably due to less protective spasm. This curve shows the marked inhibitory phases demonstrated in chart 1. Filling was discontinued when the patient complained of pain (*P*), and an appreciable interval elapsed before he could start an expulsive reaction. This was assisted by contraction of the abdominal wall, which raised the pressure 20 mm. of mercury. As the

bladder went into active contraction, several waves appeared, inaugurating the response of the detrusor muscle, which is represented by the usual uninterrupted vertical line, in this case broken by inhibition which was being rapidly overcome but still showed its effect on the early phase.

Curve *C* shows what is believed to be the true condition, a rather active curve and early expulsive reaction. While the expulsive pressure was still rising, the patient was told to relax the bladder and try not to void. No fluid escaped around the catheter and, in spite of the filling which was continued to maintain a stretch stimulus, the pressure fell off in a series of steps during the introduction of 140 cc. At this point the desire to void overcame the inhibitory effect, and two diphasic waves preceded a typical expulsive reaction.

Such a phenomenon as that demonstrated by curve (*C*) is seen in cases of psychic urinary retention, that is, in cases in which a normal person is unable to void owing to mental distraction, fear, embarrassment, etc.; in cases of some types of postoperative retention; and in cases of urethritis, in which the patient does not void because of the fear of urethral pain. Also, coupled with early prostatic hypertrophy when a small amount of concentrated urine and a low grade urethritis markedly decreases the normally possible force and size of the stream, an inhibition associated with the knowledge and fear of urinary obstruction is a factor in the occasional complete retention which is relieved by a single catheterization.

In this experiment, as the confidence of the patient returned the inhibition was lost. However, the stimulation of the first filling, increasing the tone of the musculature of the wall of the bladder, is a factor to be noted in the increased excitability of the bladder shown in tracing *C*.

These three cystometrograms demonstrate the value of repeating the examination to rule out psychic influence which otherwise could produce a curve that one might think due to incompetence or decompensation of the muscle or to faulty innervation.

Cystometrograms of patients with dysuria were next studied to find out what part inhibition, or the lack of it, played in explaining the symptomology. These, on the basis of the conditions presented by the patients, have been placed in four groups which demonstrate different aspects of this problem:

1. Total transverse lesions of the cord with well established reflex activity.
2. Partial lesions of the cord showing bilateral, incomplete involvement of the pyramidal tract.
3. Cerebral lesions without signs of damage to the pyramidal tract.
4. Local lesions of the bladder, of which there were two types: (*a*) compensating hypertrophy of the wall of the bladder behind an obstruction and (*b*) a local lesion of the bladder without obstruction of the outlet or hypertrophy of the wall.

There were three records in the first group, eight in the second, five in the third and a large number from the urologic clinic in the fourth. An example from each group is given.

Chart 3A shows the curve for a patient with a complete traumatic transverse lesion of the cord at the level of the eleventh and twelfth thoracic segments, of three years' duration. Automatic micturition commenced three months after the accident. At the time of examination the bladder showed no infection. It was emptied completely but frequently. (Such a patient does not necessarily carry residual urine, though a small amount is common. A larger amount of residual urine may occur, but it is associated with changes in the wall of the bladder.) Examination showed that all sensations were lost up to the inguinal ligament on both sides. The reflexes in the lower extremities were increased, and clonus and a Babinski sign were present bilaterally. The patient had no sensation of fullness in the bladder except a dull feeling in the lower part of the abdomen and no desire to void. If he allowed the bladder to become over full, it emptied spontaneously without his knowledge, but he had found that he could prevent this accident by rubbing or pulling the penis or by pressure on the lower part of the abdomen in

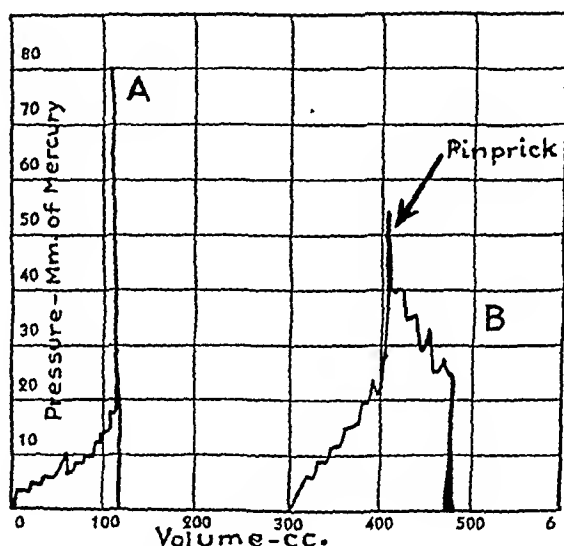


Chart 3.—A, cystometrogram of a patient with a complete traumatic transverse lesion of the spinal cord. B, a cystometrogram of the same patient showing the response to a pinprick.

the earlier stage of filling, thus precipitating the reaction at a convenient time. Stimulation of the sole of the foot was also effective in producing an emptying contraction of the bladder.

The curve shows high pressure and low volume, and when the patient was asked to try to relax the bladder no effect was produced. The second curve shows the effect of a sharp pinprick, that is, the effect of a painful type of stimulus to the glans penis during the response of the detrusor muscle, which is seen to subside in a series of steps (drum moved by hand). "Painful" stimulation of the sole of the foot had a similar effect, but no effect was produced from such nociceptive stimulation of the anterior wall of the abdomen.

These two curves show that a bladder released from cerebral control can regain tone and function satisfactorily (with no residual urine or only a small amount) and not require catheterization, which

would cause infection, and that painful stimuli in such a bladder reflexly can inhibit the contraction of the wall when cerebral inhibition is impossible. A comparison of these cystometrograms with those made in a case in which there was no lesion of the spinal cord shows conclusively that the inhibitory reflex center is in the cord and may be stimulated by the cerebrum or peripherally below a complete section of the cord.

The higher percentage of postoperative retention following perineal operations can be explained in part on the basis of cystometrogram *B* in that the first act of urination is a depression of the perineum which

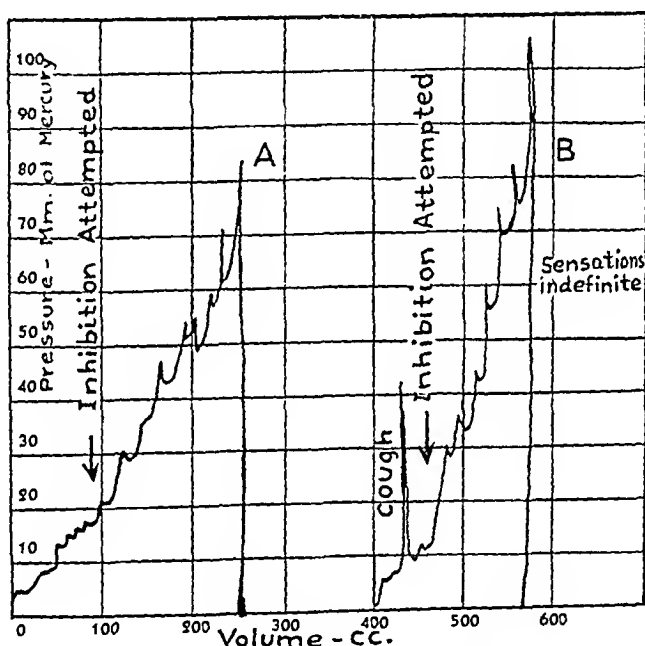


Chart 4.—*A*, cystometrogram of a patient with spasticity and weakness of both lower extremities, some ataxia and complete block of the spinal cord. *B*, cystometrogram of a senile patient with marked arteriosclerosis and impairment in his mental status.

would cause a pain stimulation type of reflex inhibition in a comparable manner to pinprick (curve *B*) and so allow overdistention of the bladder.

Curve *A* on chart 4 is the cystometrogram of a patient who on neurologic examination showed spasticity and weakness of both lower extremities, which were more marked on the left, some ataxia, but no sensory loss, and a complete spinal block to iodized poppy-seed oil 40 per cent. The reflexes were hyperactive on both sides, with clonus and a positive Babinski sign bilaterally. The patient complained of urgency and incontinence of urine for six months, and at operation a fibroblastoma of the spinal meninges extending from the eighth to the tenth dorsal segment was found. The curve shows small volume, high pressure and feeble inhibitory power.

Curve *B* on chart 4 is the cystometrogram of a senile patient who presented evidence of marked arteriosclerosis and general impairment in his mental status. He had frequency, marked symptoms of urgency and enuresis, for which a urologic examination was requested. This revealed no infection and no anatomic variation in the bladder or urethra, but again the curve shows an imperfectly controlled reaction of the bladder to filling.

Release of inhibition demonstrates itself either as frequency and urgency of urination or, in its more exaggerated form, as incontinence.

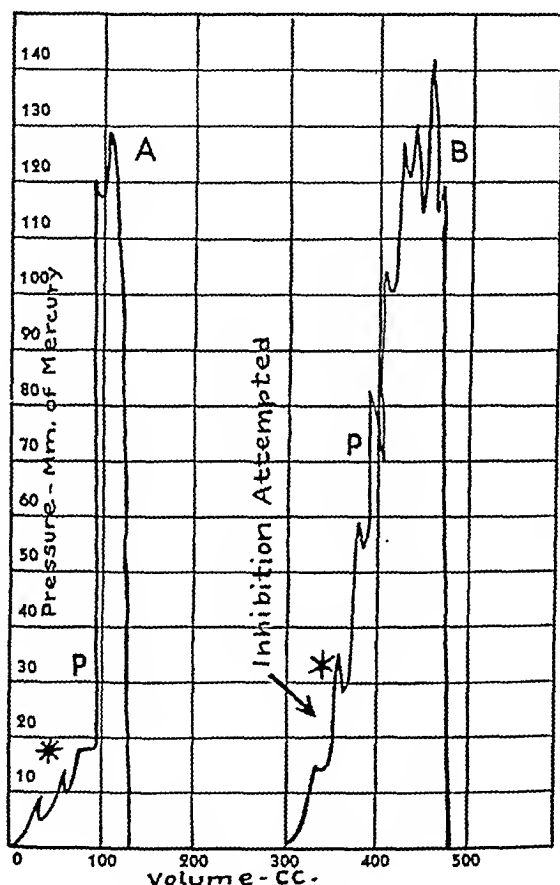


Chart 5.—Cystometrograms of a patient with a Hunner ulcer of the bladder.

varying from a continuous drip to the involuntary expulsion of small amounts of urine. Single curves for two patients, one with spinal block and the other with an inefficient cerebrum, are presented on one chart to point to the similarity of effect on bladder control when inhibition is attempted. In the case of senility (curve *B*), catheterization would prolong the frequency or incontinence by adding local reflex irritability. Such irritation being omitted, the prognosis is good on improvement of cerebration, often adversely influenced by absorption of infection.

The curves for patients with local lesions of the bladder present features identical with those illustrated in the two foregoing groups, that is, a rapidly rising curve with only slight inhibitory phases. Two curves from this group, however, are shown to illustrate special points.

* Curves *A* and *B* in chart 5 were made from the same patient, who suffered from a Hunner ulcer of the bladder. Curve *A* shows the typical early and powerful expulsive response, and *B* has been included to show the effect of a maximal inhibitory effort on this response. It will be observed that although inhibition cannot stop the powerful contraction of the bladder, it does produce a modification which is essentially a resolution of this expulsive contraction into a series of diphasic waves of increasing amplitude. That is, the response of the detrusor muscle is represented by a compound of fused diphasic waves. From a clinical standpoint, the result of asking the patient to inhibit while effecting hydraulic distention of such a bladder is graphically portrayed. It assists in increasing the capacity in relation to a contracted, high pressure. In *B*, owing to the stimulation of the filling, *A*, one would expect an immediate higher pressure but associated with a smaller capacity. Filling was discontinued as soon as the expulsive contraction commenced, to avoid effects from this cause.

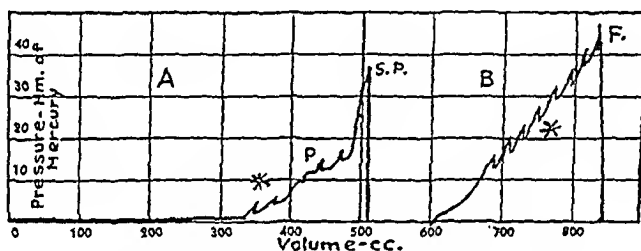


Chart 6.—Cystometrograms of a patient with an enlarged prostate which obstructed the opening of the bladder.

The cystometrograms in chart 6 were made in a case in which the opening of the bladder was obstructed by an enlarged prostate gland and 900 cc. of uninfected urine was retained in the bladder. From the standpoint of inhibition, *A* shows the flat curve and also the steplike ascent. Curve *B* is higher at the onset owing to the stimulation of the first filling and the patient's becoming reassured. It is interesting to note the sensations first desire to void (indicated by an asterisk), pain (*P*) and severe pain (*SP*). The delay of the first desire to void is associated with the flat curve of inhibition and becomes normally placed (at 150 cc.) in curve *B*. This cystometrogram was carried out only sufficiently to determine these motor and sensory points.

These cystometrograms definitely show the desirability of making two curves at the time of the first cystometric examination in that *A* could readily be interpreted as indicating a neurogenic bladder without *B* to correct the sensation readings. The plateau in *A* we associated with some muscular decompensation exhibited by the 900 cc. of uninfected residual urine. Such a normally innervated musculature^{1b} always

responds to the stimulation of filling by decreased capacity and high pressure, as is frequently observed in irrigation of the bladder and at cystoscopic examinations in our daily practice.

COMMENT AND SUMMARY

It has been shown that the normal subject can modify the reaction of his bladder at will over a considerable range of filling and that this may take the form of inhibition. The voluntary inhibitory effect is exaggerated in the presence of local pain, and it is further shown that a painful stimulus applied to somatic areas closely related to the sacral segments will produce inhibition of the bladder in a patient with a transverse lesion low in the spinal cord.

Voluntary inhibition is completely absent in a person with a transverse lesion of the spinal cord, and it is reduced in a subject whose main neurologic symptoms indicate partial damage of the pyramidal tract. It would appear, therefore, that descending pathways mediating inhibitory influences have also been damaged. Since voluntary inhibition is abolished in a person with a lesion as low as the eleventh or twelfth thoracic segment, the final pathway for this effect must be through nerves leaving the cord below that level and not through the hypogastric nerves. This is supported by the observation that reflex inhibition has a focal point of stimulation representing this area of the cord and that stimulation of areas more closely related to the hypogastric nerves has no such effect.

Inhibitory power is reduced in certain cerebral lesions, and here the interference would appear to be with centers originating the inhibitor impulses. Impairment of control in a person with a local lesion of the bladder is regarded as an "escape" phenomenon; that is, the irritability of the bladder mechanism overcomes the inhibitory control.

The bladder in the stage of reflex activity following total section of the cord above the sacral segments differs from the normal bladder only in the absence of sensation and in the lower volume it will tolerate; otherwise the mechanism is entirely coordinate and adequate. The contraction of the detrusor muscle always precedes relaxation of the sphincter muscle, as shown by the high pressure attained before fluid begins to escape. In order that the bladder may empty completely, the sphincter muscle remains relaxed until the end of the contraction of the bladder. Relaxation of the sphincter muscle is therefore not the primary event in micturition but appears rather to be dependent on and conditioned by the expulsive contraction of the detrusor muscle.

Voluntary inhibition was invoked to study the response of the detrusor muscle, and it was found that under this influence it undergoes a resolution into a series of diphasic waves showing a tendency to fuse.

Similar waves were often observed to precede the expulsive reaction and appear to be due to transient inhibition of its early phase. This observation supports the view that the response of the detrusor muscle is a motor tetanus and therefore is produced by an increase in the number of efferent volleys of nerve impulses impinging on the muscle in a given interval of time.

In view of the marked acceleration of the curves in certain of the conditions demonstrated in this paper, it would appear that the filling of the normal bladder depends on a graded inhibition of a tendency which the bladder possesses to go into early and active contraction. Evidence has already been presented by Denny-Brown and Robertson² that the contraction of the detrusor muscle is due to a process of wave summation and also that inhibiting influences operate at the sacral level. Our observations support this view. It is clear also that a pathway through the hindbrain is not essential for the emergence of an expulsive reaction, though such a "long circuit" pathway may exist in the intact animal as an additional means of facilitating higher control and coordination of the bladder.

It seems reasonable now to suggest that the reflex mechanism in the sacral portion of the cord operates in the following manner: As distention proceeds, the progressive stretch of the wall of the bladder elicits a progressively increasing number of afferent impulses. These pass back to the cord and, in the absence of a "blocking" effect, immediately spread over to the efferent side and soon build up a tetanic level of stimulation which produces an expulsive reaction. The function of inhibition is to regulate this mechanism according to the needs of the patient by imposing a variable block between these two pathways.

Learmonth³ put forward the view that the contraction of the detrusor muscle and the relaxation of the involuntary sphincter muscle are carried out by separate nerves, and he described the hypogastric nerve as a "filling" nerve and the pelvic nerve as an "emptying" nerve. This carries with it the assumption that the anatomic division into sympathetic and parasympathetic systems coincides with mutually exclusive physiologic functions. That this is not so in other parts of the body in animals has been shown by many observers (Dale and Gaddum,⁴ Heinbecker⁵ and others) and in relation to the bladder by MacDonald and McCrea.⁶ Furthermore, clinical experience lends little support to the

2. Denny-Brown, D., and Robertson, G.: *Brain* **50**:149 and 397, 1933.

3. Learmonth, J.: *Tr. Med.-Chir. Soc. Edinburgh*, 1931-1932, p. 43; in *Edinburgh M. J.*, April 1932.

4. Dale, H., and Gaddum, J. H.: *J. Physiol.* **70**:109, 1930.

5. Heinbecker, P.: Personal communication to the authors.

6. MacDonald, A. D., and McCrea, E. D. A.: *Quart. J. Exper. Physiol.* **20**:379, 1930; *Brit. J. Urol.* **6**:119, 1934.

theory of equal and opposite functions for the so-called "presacral" and "pelvic" nerves.

Since Eccles' ⁷ work on the selective action of the superior cervical sympathetic ganglion cells, showing that the same preganglionic stimulation produces effects both of facilitation and of inhibition in different groups of postganglionic fibers, another explanation seems possible. According to this theory, the preganglionic discharge set up reflexly by filling the bladder would be differentiated by the cells of the pelvic ganglion, inhibitory impulses being set up in some postganglionic fibers and excitator impulses in others, these passing respectively to the sphincter and the detrusor muscle. Such a mechanism would be more convincing in explaining the dependence of the relaxation of the sphincter muscle on the activity of the detrusor muscle.

It is further pointed out here that the involuntary activity of the bladder is only relative in the normal subject and that "willed" control of this "involuntary" system is exerted through the power of inhibition.

7. Eccles, J. C.: *J. Physiol.* **85**:209, 1935.

EFFECT OF ANESTHETICS ON LYMPHATIC ABSORPTION FROM THE PERITONEAL CAVITY IN PERITONITIS

AN EXPERIMENTAL STUDY

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One of the most important, if not the principal, factor in peritonitis is the accompanying toxemia. Since the success or failure of treatment depends largely on measures designed either to neutralize the toxins as formed or to prevent their absorption into the systemic circulation, it is natural that a great deal of interest has been evinced in the manner in which these toxins enter the systemic circulation.

A survey of the literature reveals that the absorption from the peritoneal cavity is as yet not thoroughly understood. There are many factors which affect the rate of absorption, and there is more than one avenue of escape of material from the peritoneal cavity. While it is not the purpose of this report to comment on how material, whether it is particulate, crystalloid or a colloid solution, leaves the peritoneal cavity, a brief summary of the evidence at hand may be of interest.

The first study on peritoneal absorption is generally credited to von Recklinghausen¹ in 1863. Using silver nitrate stains, he stated that particulate material entered the lymphatics through definite openings, or "stomas," between the endothelial cells. This view was generally accepted until MacCallum² in 1903, by means of painstaking work, disproved the presence of these "stomas" and concluded that particulate material passed directly through the living cytoplasm of the endothelium. He also expressed the belief that respiratory movements were an important factor in promoting this absorption.

This view has since been supported by other physiologists, especially Cunningham,³ who made a number of contributions to the literature on this subject and in 1926 summarized his views, together with a survey of the literature published up to that time. He agreed with

From the Department of Research Surgery, Temple University School of Medicine.

1. von Recklinghausen, F. I.: *Virchows Arch. f. path. Anat.* **26**:172, 1863.

2. MacCallum, W. G.: *Anat. Anz.* **23**:157, 1903; *Bull. Johns Hopkins Hosp* **14**:105, 1903.

3. Cunningham, R. S.: *Physiol. Rev.* **6**:242, 1926.

MacCallum that particulate material passes directly through the cells, and by an ingenious study of absorption in fetuses he showed that respiratory movements were the predominant factor.

It is the consensus among contributors to this subject that the diaphragmatic peritoneum plays the only significant rôle in the removal by the lymphatics of particulate material from the peritoneal cavity and that the mediastinal lymph nodes serve to collect the lymph draining from the peritoneal cavity. Crystalloids and colloids are almost wholly taken up by the venules of the omentum.

Buxton and Torrey⁴ in 1906 injected nucleated erythrocytes and suspensions of living bacteria into the peritoneal cavity and timed their appearance in the blood and lymph streams.

In 1914 and 1915 Dandy and Rowntree⁵ studied the absorption of phenolsulfonphthalein from the peritoneal cavity. They found that it appeared in the blood stream in from two to four minutes, in the urine in from four to six minutes and in the lymph stream (thoracic duct) in from twenty to fifty minutes. They also studied the effect of posture on drainage and discovered that the rate and amount of absorption was about equal in all postures except pelvis down (Fowler position), in which position the absorption was uniformly about 15 per cent less. They summed up the literature on absorption from the peritoneal cavity that had been published up to that time and concluded that the lymphatic absorption of fluids was greatly overestimated, that most of the absorption takes place through the blood stream and that this holds true for both bacteria and toxins. All their studies were made on normal animals, i. e., in the absence of peritonitis.

In 1925 Steinberg,⁶ in a study of absorption from the peritoneal cavity in dogs, stated that drainage of the thoracic duct has no value in the treatment of peritonitis. In 1927 Drinker and Churchill,⁷ wishing to make intravital studies of the capillaries, tried a great many kinds of dyes, inks and colloidal graphite solutions and found that hydrokollag 300, a graphite base for printer's ink, when neutralized and diluted with a saline-acacia solution, gave the best results. Many of the particles are smaller than erythrocytes, and there is no tendency to plug the lymphatics by clumping, as other inks do, or to diffuse out into the perilymphatic tissue spaces, an annoying feature of the soluble dyes.

4. Buxton, B. H., and Torrey, J. C.: *J. M. Research* **15**:55, 1906.

5. Dandy, W. S., and Rowntree, L. G.: *Beitr. z. klin. Chir.* **87**:539, 1915; *Ann. Surg.* **59**:587, 1914.

6. Steinberg, B.: *J. Exper. Med.* **42**:83, 1935.

7. Drinker, C. K., and Churchill, F. D.: *Proc. Roy. Soc., London, s.B* **101**: 462, 1927.

Florey in 1927⁸ used hydrokollag 300 and declared it to be far superior to many other substances which he had used. As a result of his experiments, he concluded that intra-abdominal pressure, as affected by the activity of the animal and by the rate and depth of respiration, plays a big rôle in the removal of particulate material from the peritoneal cavity. He also made the suggestive remark that experiments performed on the relative rates of absorption through the lymphatics in anesthetized animals give a far from accurate picture of what really happens in the normal animal.

In 1927 Higgins,⁹ wishing to study the absorption of particulate material from the peritoneal cavity of dogs, discovered that nothing definite was known of the lymphatic system of the dog. Using hydrokollag 300, he worked out the lymphatic routes draining the peritoneal cavity in these animals. He found five routes through which particulate material may be removed: (1) the sternal route—the most important—which traverses the substernal aerolar tissue and empties into the lymph nodes between the first and the second rib and thence into the thoracic duct or the right lymphatic duct just at or before the venous confluence; (2) the pulmonary route, consisting of lymphatics and nodes in the anterior mediastinum and bronchial nodes at the base of the lungs; (3) the thoracic duct itself; (4) the retroperitoneal route, and (5) the direct peritoneal route. The sternal route transmits about four fifths of the entire amount of the particulate material. He then studied the rate of absorption of this material; this phase of his work will be referred to later. Other investigators, meanwhile, were studying the subject from other points of view.

Brown in 1927¹⁰ reported experimental work in dogs and cats which seemed to show that lymphatic drainage of the diaphragm is only subsidiary to the removal of the material by the venules of the omentum and mesentery. He expressed the belief that lymphaticostomy, which had been advocated as a method of preventing toxins from entering the circulation, was of no value in spreading peritonitis. Similar findings were reported by Poynter,¹¹ who felt that the venules of the omentum were the chief avenue of exit of toxic material from the peritoneal cavity, although he admitted that of the lymphatic drainage, the diaphragmatic route is the only one of any consequence.

8. Florey, Howard: *Brit. J. Exper. Path.* **8**:479, 1927.

9. Higgins, G. M., and Graham, R. S.: *Lymphatic Drainage from the Peritoneal Cavity in the Dog*, *Arch. Surg.* **19**:453 (Sept.) 1929.

10. Brown, K. P.: *Brit. J. Surg.* **15**:528, 1927.

11. Poynter, C. W. M.: *Proc. Staff Meet., Mayo Clin.* **2**:263, 1927.

David in 1927¹² and David and Sparks in 1928¹³ experimented with injections of *Bacillus coli* into the peritoneal cavity. They found that bacteria were absorbed into the blood stream and lymphatics at practically an equal rate, that plastic exudate cuts down the rate and amount of absorption and that when the exudate is well developed absorption into the blood stream or lymphatics practically ceases. However, the presence of a transudate induced by hypertonic dextrose solution injected into the peritoneal cavity causes rapid absorption into both blood stream and lymphatics. This last statement bears out the clinical observation that so-called "wet" types are subject to a higher mortality than "dry" types of spreading peritonitis.

In summarizing all these conflicting statements several points are obvious:

1. Observations which are carried out on normal peritoneum have little value in helping one to estimate the rate and amount of absorption of toxic material from an abdomen which is the seat of a spreading peritonitis.

2. Prior to Higgins'¹⁴ fine work on dogs, experimental studies in these animals on the lymphatic drainage from the abdomen with regard to the efficacy of lymphaticostomy are of little or no value because the thoracic duct plays such a minor rôle.

3. There is a difference in the behavior of crystalloids as compared with that of particulate material in that they are removed with equal facility by both the blood and the lymph streams.

4. Although Florey pointed the way with his experiments, practically none of the other investigators considered the effects of diaphragmatic activity on the rate of absorption of toxic material from the peritoneal cavity until Higgins followed up this suggestion in 1929.

Using ether exclusively, Higgins found that the graphite appeared in the lymphatics in approximately three minutes. After phrenicectomy, he found that it required from eight to fifteen minutes. Also, if the abdomen were opened and the omentum excised, or if the intestines were merely handled and then replaced, the appearance of the graphite was delayed likewise to from eight to fifteen minutes. However, if the omentum was excised and several days allowed to elapse before the graphite experiment was performed, the rate of absorption returned to normal. He also found that it took from thirty to forty minutes for graphite to appear in the thoracic duct and that after phrenicectomy the appearance in the duct was delayed from one and a half to three hours.

12. David, V. C.: *Surg., Gynec. & Obst.* **45**:287, 1927.

13. David, V. C., and Sparks, J. P.: *Am. Surg.* **88**:672, 1928; *Tr. Am. S. A.* **46**:362, 1928.

14. Higgins, G. M., and Murphy, G. T.: *Anat. Rec.* **40**:15, 1928.

Since many patients with spreading peritonitis complicating acute perforative appendicitis are operated on, either inadvertently or designedly, during the early stages of the disease, I wished to ascertain, if possible, what effect was exerted by the anesthetic on the rate of lymphatic absorption.

EXPERIMENTAL WORK

To this end a series of animals was first studied to determine the rate of absorption of particulate material (graphite) from the normal abdomen. The



Fig. 1.—Incision in the chest showing the periosteum incised and partially sawed through. About two-thirds actual size.

method devised by Higgins was followed without any difficulty. The animal did not receive any breakfast the day of operation. It was fastened to the operating table, and the chest and abdomen were shaved. The chest was opened in the median line, the periosteum was split in the midline and the sternum was sawed through from the first chondrosternal joint down to the fourth rib, care being taken not to saw through the inferior layer of the periosteum, which was incised with a knife. This exposed the substernal alveolar tissue, which contains the sternal lymphatics, nodes and blood vessels. If one carefully stays in the midline there is

little danger that the dura will be punctured in the procedure. From 8 to 10 cc. of graphite was then injected into the free peritoneal cavity, and the time of injection was noted. The animal was watched until the graphite appeared in the sub-sternal nodes and lymphatics, when the time of appearance was noted.

The graphite used was prepared as follows (Higgins and Murphy's modification of Drinker and Churchill's original method):

Hydrokollag 300 is a colloidal preparation of graphite containing ammonia and a small amount of cherry gum as a protective colloid. It mixes freely with blood serum and acacia without agglutinating. When received, it is a thick syrup with



Fig. 2.—Incision in the chest showing the sternum split and the mastoid retractor separating the halves, exposing the substernal areolar tissue. About two-thirds actual size.

a sediment at the bottom. In preparing it for use it is first shaken and thoroughly stirred up. One hundred and twenty grams is weighed out, and 2 cc. of saturated solution of sodium hydroxide in 250 cc. of distilled water is added. This mixture is then placed high over a Bunsen flame and heated gently while a stream of air is bubbled through it. This procedure, which drives off the ammonia, requires about four hours. The mixture is then diluted with an equal quantity of a saline-acacia mixture (12 per cent acacia in a 18 per cent solution of sodium chloride). The entire mixture is centrifugated at moderate speed for ten minutes. The upper

four fifths of the solution is pipetted off into a clean sterile flask, and the remaining liquid is pipetted into a second flask. The cake in the bottom of the tube is discarded. The contents of the second flask are recentrifugated for ten minutes, and the upper four-fifths is again removed and added to the first flask. This process is repeated until practically all the liquid is recovered, the remainder being discarded. All the large particles and lumps are removed by this method. This mixture will keep in the refrigerator for from two to three months.

A total of fifty-nine dogs were used in these experiments. Of these eleven died during the course of the experiments, either from accidentally rupturing the



Fig. 3.—A substernal lymph node is shown at *x*, filled with graphite. About one and two-thirds actual size.

pleura or from an overdose of anesthesia; in two animals the graphite was injected into the falciform ligament; in one, it was injected into the urinary bladder, and in one, the graphite was discharged into the lumen of the intestine. These were discarded, leaving forty-six animals available for study.

The effect of the anesthetic on the rate of lymphatic absorption from a normal peritoneal cavity was first studied briefly. These results are shown in table I, and the results under ether anesthesia agree closely with those of Huggins, who used ether exclusively in all his experiments. The slightly longer times of appearance in my experiments (from five to seven minutes) compared with his (from three

TABLE 1.—*Effect of Anesthetic on the Rate of Lymphatic Absorption from a Normal Peritoneal Cavity*

Anesthetic	Time of Appearance, Min.	Average Time of Appearance, Min.
Ether.....	7, 5, 7	6.3
Spinal: procaine hydrochloride (80-120 mg.).....	13, 12, 15	13.3
Local (for incision in chest).....	No graphite in 2 hr.	
Procaine hydrochloride (1%).....	No graphite in 2 hr.	0 under 2 hr.
Sodium amytal (35 mg. per Kg. of body weight intraperitoneally).....	38, 50, 23	37.0

TABLE 2.—*Results of Graphite Absorption Tests on Dogs with Local Peritonitis **

Duration of Peritonitis After Ligation of Appendix, Hr.	Time of Appearance of Graphite, Min.	Average Time, Min.
24.....	11.0, 9.5	10.0
48.....	20.0	20.0
72.....	30.0, 22.0	26.0
96.....	36.0, 45.0	40.5

* Ether anesthesia was used.

TABLE 3.—*Results of Graphite Absorption Tests on Dogs with Spreading Peritonitis of Twenty-Four Hours' Duration*

Anesthetic	Time of Appearance of Graphite, Min.	Average Time, Min.
Ether.....	14, 17.5, 28, 30, 25	22.9
Spinal: procaine hydrochloride (80 mg.).....	35, 25, 31, 25	29.0
Sodium amytal (35 mg. per Kg. of body weight intraperitoneally).....	35, 45, 45, 45	42.5

TABLE 4.—*Results of Graphite Absorption Tests on Dogs with Spreading Peritonitis of Twenty-Four Hours' Duration*

Anesthetic	Time of Appearance of Graphite, Min.	Average Time, Min.
Ether.....	20, 19, 17, 24, 37, 27	24
Spinal: procaine hydrochloride (80 mg.).....	40, 43, 37, 35 None after 90 min.	49
Sodium amytal (35 mg. per Kg. of body weight intraperitoneally).....	48, 88 None after 90 min.	75
Spreading Peritonitis of 96 Hours' Duration		
Ether.....	46	



Fig 6—Anterior wall of the chest reflected lateral so as to be viewed from behind X shows the substernal lymph nodes filled with graphite.



Fig 7—Same as figure 6 in another animal

SUMMARY

A study is presented of the effect of different anesthetics on the absorption of particulate material from the peritoneal cavity of experimental animals, by way of the lymphatics, in (*a*) normal animals, (*b*) animals with local peritonitis, (*c*) animals with spreading peritonitis of twenty-four hours' duration and (*d*) animals with spreading peritonitis of forty-eight hours' duration.

The results of this study show that in normal animals and those with either local or spreading peritonitis the greatest stimulation to lymphatic absorption (and so to toxic absorption) is produced by the anesthetics which most stimulated the activity of the diaphragm. It is believed, therefore, that local infiltration or regional block anesthesia with 1 per cent procaine hydrochloride or low spinal anesthesia with procaine hydrochloride is the method of choice for operations in the presence of peritonitis.

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ENCEPHALOGRAPHY WITH ANESTHETIC GASES

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The experimental background for encephalography with the use of anesthetic gases has been reported in previous articles.¹ The characteristics of the severe and prolonged reaction following the injection of air and the attempts of various workers to find a suitable substitute were discussed. The use of oxygen by Jüngling² in 1922, by Denk³ in 1923 and more recently in Penfield's clinic,⁴ as well as the trial of carbon dioxide, nitrogen and helium by Liberson,⁵ were mentioned. A review of the literature on the experimental trial of various opaque fluids was also presented. A theoretical consideration of the various factors involved in the problem of encephalography led to the establishment of certain criteria. In this connection it occurred to me that an anesthetic gas might approximate the ideal desired. In brief, it seemed possible that even potent anesthetic gases might prove safe, since only a limited amount of gas may be injected, and this would be relatively inert except as absorbed. Any sedative or narcotic effect would be secondary to its absorption and concentration in the central nervous system. The handling of the gas and the roentgenographic results would be comparable to those achieved by the use of air. The duration of the presence of the anesthetic gas would depend on such factors as its rate of diffusion and solubility in the cerebrospinal fluid and lipoids of the brain. To investigate these possibilities a method was devised for testing various gases by injection into dogs, air being used as a standard of comparison. Eight anesthetic gases as well as oxygen were studied

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This work was carried out in the service of Dr. Howard C. Naffziger at the University of California Hospital.

1. Aird, R. B.: (a) Experimental Encephalography with Anesthetic Gases, *Proc. Soc. Exper. Biol. & Med.* **31**:715-717, 1934; (b) *Arch. Surg.* **32**:193-217 (Feb.) 1936.

2. Jüngling, O.: Roentgenography of Cerebral Ventricles, *Zentralbl. f. Chir.* **49**:835-836, 1922.

3. Denk, W.: Ueber Encephalographie und ihre Ergebnisse, *Ztschr. f. ärztl. Fortbild.* **20**:426-430, 1923.

4. Cone, W.: Personal communication to the author.

5. Liberson, F.: Use of Various Gases in Encephalography: Summary of Two Hundred and Ten Cases Using Simultaneous Displacement Apparatus, *Am. J. M. Sc.* **185**:478-484, 1933.

in this manner. Of this group, nitrous oxide and ethylene seemed promising. Their injection appeared entirely safe, their narcotic effect was slight but definite, good roentgenographic results were obtained, irritative effects were minimal and no untoward after-effects were observed. Special control studies were then made. No neuropathologic changes were found in the brain, cord or meninges after repeated injections of these gases. Cytologic and pressure studies were made on the spinal fluid after injection, and the results were found to be essentially comparable to those obtained with air. The conclusion was reached that nitrous oxide and ethylene were safe and that their trial in man was justified. The present report presents the results obtained with these gases in encephalography on human beings.⁶

METHODS

Technic of Injections.—The method and technic of encephalography adopted for this study were essentially the same as those previously used in this clinic with air.⁷ The method had proved satisfactory, and it was felt that a fairer comparison of the gases could be made if the same method were used. This method consisted of a simultaneous drainage of cerebrospinal fluid and its replacement with gas by means of two spinal punctures in the lumbar interspaces. The gas was injected slowly and at constant pressure (approximately the initial pressure) through the upper needle. A Boullite manometer, connected by tubing to the injecting syringe and needle, was used to control the pressure of injection. The cerebrospinal fluid drained freely during the procedure from the lower needle. The injections were done with the patient in the sitting position and under anesthesia. Tribromethanol in amylene hydrate and procaine hydrochloride locally were used for adults, while the induction of anesthesia with ether proved adequate for children. As complete an exchange of gas and fluid as possible was effected in all instances.

The only modification of this technic for the anesthetic gases was the use of a closed injection system to prevent the escape or dilution of the gas to be injected. This closed system consisted of a rubber bag as a reservoir for the anesthetic gases, connected to the syringe and tubing by means of a three way petcock (fig. 1). Turning of the petcock allowed in turn for the filling of the syringe from the bag and then the injection of the contents of the syringe under controlled conditions of pressure and volume measurement through the upper needle, the manometer being connected to the injection system as already mentioned. Small rubber tubing with adaptors for connecting the needle and the petcock, a T or Y glass tube for the side connection to the manometer and a rubber bag with a three way petcock

6. Both nitrous oxide and ethylene have been tried in ventriculography. Although the results were satisfactory, studies along this line have not been continued. Since ventriculography is ordinarily tolerated better than encephalography and the air may be removed if it does cause a severe reaction, and also since ventriculography is usually reserved for cases in which operative intervention quickly follows, the use of the anesthetic gases has not the same advantages in this procedure as in encephalography.

7. Stone, Robert S., and Jones, O. W., Jr.: Encephalography: A Review of One Hundred and Thirteen Cases, and a Report of Post-Mortem Studies on the Injection of Air, *Radiology* 21:411-419, 1933.

connected, as shown in figure 1, constitute the necessary equipment. An additional rubber tube with a small piece of cotton packed and fixed inside the tubing as a bacterial filter suffices to connect the tank and bag for filling purposes. The rubber equipment should be boiled in water for at least three minutes before it is used and should be conveniently wrapped separately in a sterile towel.

Roentgenologic Technique.—After the injection of gas the patient was placed on his back and transferred in this position to the x-ray table. Anteroposterior and horizontal transverse views were taken for visualization of the anterior horns, and the films were immediately examined to determine whether or not adequate filling had been obtained. If the injection merited continuation of the roentgen series, the patient was turned so that, successively, the other three sides of the head (occiput and right and left sides) were uppermost. Thus, even though the filling was not complete, each portion of the ventricular system was filled with the gas. Two roentgenograms were taken in each position; one was a vertical projection



Fig. 1.—Sketch illustrating the setup and method of closed system of encephalographic injection of anesthetic gases.

made with the x-ray tube above the patient's head, with the aid of the Potter-Bucky diaphragm, and the second, a horizontal-transverse projection made with the tube at the side of the patient's head, with the aid of a portable Lysholm grid. In this fashion visualization of each portion of the ventricular system is possible in two different planes. Such "geometrical" views have been found to have a distinct advantage in the localization of any positive roentgenographic findings.⁸ The sequence of taking the films was occasionally varied, and ordinarily the region under suspicion was studied first (after the two initial projections with the occiput down) in order to take advantage of all the gas possible.

8. Naffziger, Howard C.: Personal communication to the author. Stone and Jones.⁷

A satisfactory routine which involves a minimum of turning the patient and changing the position of the x-ray tube is as follows (with the patient lying down):

- A. Occiput down (for visualization of the anterior horns and third ventricle)
 1. Anteroposterior projection
 2. Horizontal transverse projection
- B. Brow down (for visualization of the occipital horns)
 3. Horizontal transverse projection
 4. Postero-anterior projection
- C. One side of the head down—the side opposite to that under suspicion, as determined clinically or by study of the first two views—(for visualization of the temporal horn and the body of the uppermost lateral ventricle)
 5. Vertical lateral projection
 6. Horizontal anteroposterior or postero-anterior projection
- D. Other side down (for visualization of the other temporal horn and lateral ventricle)
 7. Horizontal postero-anterior or anteroposterior projection
 8. Vertical lateral projection
- E. Repeat or special views, as determined by study of the wet films previously taken

Bacteriologic Control Studies.—Nitrous oxide and ethylene from anesthetic tanks were run through a sterilized system of tubing, petcock and needle similar to that used in the encephalographic procedure, and each gas was bubbled into flasks of broth for ten seconds and one minute, respectively. One hundred cubic centimeters of air was likewise bubbled through broth, a sterile Luer syringe being used to force it through the sterilized encephalographic equipment as before. Subsequent plating and the original broths failed to show growth in four days of incubation.

In spite of these negative results, as an extra precaution a small cotton plug was inserted into the tubing used for filling the bladder. Thus a bacteriologic filter was provided which was sterilized with the tubing for each procedure.

ENCEPHALOGRAPHY WITH AIR AS A STANDARD OF COMPARISON

To evaluate properly the results obtained with the anesthetic gases in this study, it seemed essential to know the comparative results obtained with air, the method of injection being fundamentally the same.

Twelve consecutive patients on whom well controlled encephalographic studies with air had been made were subjected to roentgenographic follow-up studies comparable to those made when the anesthetic gases were used. Since the results in this group are also representative of those obtained with the injection of air in general and of the results obtained in this clinic by means of the technic described, they will be discussed in detail. All the encephalographic injections were performed with the patient under anesthesia. Ether was administered to the chil-

dren throughout the period of injection and again during the period of roentgenography to ensure satisfactory results. Tribromethanol in amylene hydrate was used for the adults.

Headaches, moderate to severe in intensity, persisted for an average of one and a half days after the injections, while slight headache, associated particularly with movement or sitting up, lasted for approximately seventy-two hours. Sedatives were required repeatedly by all patients for an average of nearly three days. Nausea usually continued through the first day, and hypodermoclysis was usually necessary. Fluids by mouth and a soft diet were ordinarily tolerated by the second day. The maximum temperature reaction of the 12 patients averaged 38 C. (100.4 F.) at approximately ten hours after the injection.

The roentgenographic studies for these 12 patients were satisfactory. The pictures for 5 showed excellent filling, for 3 good filling and for 4

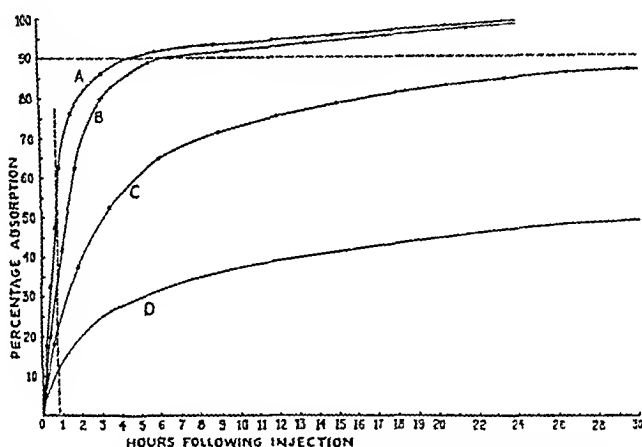


Fig. 2.—Graph showing the estimated absorption rate of gases after encephalographic injection, based on study of serial, follow-up roentgenograms with the following gases: nitrous oxide (*A*), ethylene (*B*), oxygen (*C*) and air (*D*). The ordinate at fifty minutes after injection indicates the average time required for completion of the roentgenographic phase of encephalography; the abscissa at 90 per cent indicates the point of gas absorption at which clinical relief from post-encephalographic reaction is usually obtained.

only fair filling. It should be mentioned, however, as will be brought out later, that in general as many inadequate fillings are obtained with air as with the anesthetic gases presented in this study.

As is indicated in figure 2, the absorption of air was much slower than the absorption of either of the anesthetic gases. The individual variation was great, but the average showed 50 per cent or more of air still present at twenty-four hours and approximately 10 per cent still present at seventy-two hours. Air was found to remain as long as one hundred and forty-four or one hundred and sixty-eight hours in some cases.

COMPARATIVE STUDY

Encephalography with Oxygen.—The use of oxygen in encephalography has been reported on favorably, and the results probably show about as great an improvement over the use of air as can be obtained

TABLE 1.—*Results of Encephalography with Air and Other Gases*

	Air (Under anes- thesia)	Oxygen (Under anes- thesia)	Nitrous Oxide Varied with nar- coses; occasion- ally slight pallor or cyanosis	Ethylene Varied with nar- coses; in children induction of anes- thesia alone neces- sary
Reaction to injection	(Under anes- thesia)	(Under anes- thesia)	Varied with nar- coses; occasion- ally slight pallor or cyanosis	Varied with nar- coses; in children induction of anes- thesia alone neces- sary
Ease of making roentgenograms	Usually easy; continued etheri- zation required in all children	Usually easy; continued etheri- zation required in all children	Usually easy; etherization rarely required	Usually easy; etherization rarely required
Roentgen results				
1. Satisfactory	Usually good	Usually good	Usually good with rapid x-ray technic	Usually good
2. Unsatisfactory filling				
(a) Ventricular	About 16%	About 14%
(b) Subarachnoid	About 11%	About 11%
Headache	Moderate to se- vere in all adults for average of 36 hours' dura- tion; slight, with movement for average of 72 hr.	Moderate to se- vere in all adults for 1-2 days; slight with move- ment for 2-3 days	Usually light; slight with move- ment for about 24 hr.	Usually light; slight with move- ment for about 30 hr.
Sedatives	Usually required repeatedly	Usually required repeatedly	Required one or two times only by about one half of adults	None required by half of patients; required more than one to two times by about one third of adults
Nausea and vomit- ing	Often moderate and prolonged	Often moderate and prolonged	Usually light for 4-5 hr.	Usually light for 5-6 hr.
Fluids tolerated	20 hr.	7-8 hr.	6-7 hr.	7 hr.
Diet tolerated	2d day	2d day	6-8 hrs.	7-8 hrs.
Temperature	38 C. at 10 hr.; normal in 22-30 hr.	38.2 C. at 10 hr.; usually normal in 30 hr.	38.2 C. at 8 hr.; normal in 12-24 hr.	Adults, 37.9 C. at 9 hr.; children, 38.5 C. (rectal) at 9 hr.; normal in 20-24 hr.
Pulse and respira- tion	Normal	Normal	Normal	Normal
Duration of reaction	Average of 3 days	1-3 days	Usually 12-24 hr.	Average of 30 hr.
Severity of reaction	Usually moderate to severe and prolonged in adults; light to moderate and prolonged in children	Usually moderate to severe and prolonged in adults; light to moderate in children; less prolonged than with air	Usually light in both adults and children, and only occasionally prolonged be- yond 24 hr.	Usually light in both adults and children; occa- sionally prolonged beyond 30 hr.

with ordinary gases. For the sake of comparison, encephalography with oxygen was tried on a few patients with the same technic and the careful follow-up study described in the use of the other gases. The results obtained are in essential agreement with those reported from Penfield's clinic and are presented in table 1. It may be said that in general the

reaction to oxygen, although appreciably less than the usual reaction to air, is considerably more severe and prolonged than that caused by the use of the anesthetic gases, which will be considered next.

Encephalography with Nitrous Oxide.—Encephalography with nitrous oxide was performed 11 consecutive times on 10 patients varying in age from 10 months to 49 years. The clinical reaction to the nitrous oxide was relatively slight and was strikingly less than is usually experienced after encephalography with air. Headache, from slight to moderate in severity and typically occurring in spells, persisted usually for from five to six hours after the injection. Slight headache with movement and sitting up ordinarily persisted for from twenty to twenty-four hours. Aside from 2 patients with an exceptional prolonged reaction, only 1 required a sedative after encephalography with nitrous oxide. It is, however, only fair to say in this connection that of the 7 patients not requiring sedatives, only 2 were adults and that in general children stand the procedure much better than adults.

The patients usually felt somewhat nauseated for four or five hours, and about one half of the group suffered from vomiting of mild degree. Water by mouth was tolerated from six to seven hours after injection, a liquid diet after from six to eight hours and a soft or regular diet after from twenty to twenty-four hours. The temperature usually returned to normal within fifteen or sixteen hours. The pulse and respiration reflected no untoward reaction. Aside from 2 patients with slight pallor and a third with a questionable cyanosis, none of the group showed any immediate reaction to the encephalographic use of nitrous oxide.

Unsatisfactory ventricular filling occurred in 3 instances, 2 of the unsuccessful attempts being made on the same patient. A positive diagnosis was made in 6 of the remaining 8 cases as a result of the encephalograms, the diagnoses agreeing well with the clinical findings. The encephalograms in the other 2 cases, in 1 of which the patient was suspected of having a tumor of the brain while in the other case the patient had a convulsive state of unknown etiology, were normal. Of the 8 cases in which satisfactory filling was obtained, the results were excellent in 3, good in 1 and fair in 4. In all cases the patient remained quiet throughout the period of taking the roentgenograms and the roentgenographic series was obtained without difficulty.

The rate of disappearance of the gas, as observed by comparing the final views with the initial views, was striking, and follow-up roentgenographic studies showed on the average a disappearance of about 90 per cent of the nitrous oxide in five hours. The residual amount disappeared much more slowly, and usually traces could be found up to twenty-four hours. The estimated rate of absorption of nitrous oxide

is shown in figure 2. The slower terminal absorption is perhaps best explained on the basis of impurities of relatively low solubility in the nitrous oxide. Such impurities are known to be present in the commercial nitrous oxide used for anesthetic purposes.

Since, on the average, forty-four minutes was required from the termination of the injection of the gas to the completion of the roentgenographic studies and since from 40 to 50 per cent of the gas had disappeared in this time, the absorption of nitrous oxide was considered to be too rapid to insure the best roentgenographic results. Although the period required for taking the roentgenograms might have been appreciably reduced by performing the injection in the x-ray room and proceeding without delay through the series, from twenty-five to thirty minutes would still have been required, and over this period it was estimated that approximately one third of the gas would have disappeared (fig. 2). Since any retake or special projections necessarily are taken last and these are often the most important from the standpoint of the roentgenographic diagnosis, it seemed advisable to use a gas which would be absorbed more slowly.

*Encephalography with Ethylene.*⁹—Since the solubility of ethylene is considerably less than that of nitrous oxide,^{1b} its trial in encephalography was next undertaken. One hundred successive encephalograms have been made in the University Hospital for patients with the usual conditions requiring encephalography (table 2). Their ages varied from 5 months to 56 years. Sixty-four were adults, and 36 were children (15 years of age or under).

The time required for the injection of the gas averaged ten minutes, extremes of 40 and 275 cc. of ethylene being injected. The average amount for children under 6 years of age was 82 cc.; for children from 6 to 16 it was 100 cc., and for adults (16 years and over) it was 136 cc.

No dangerous reactions were observed. The immediate reaction varied with the degree of narcosis. In 2 patients on whom the procedure of injection was carried out without anesthesia, except for a sedative and procaine hydrochloride locally, the reaction was severe and comparable to that sustained with the injection of air under the same circumstances, e. g., severe frontal headache, vomiting and perspiration. Unlike the reaction caused by air, however, this acute reaction soon passed, and although the patients were aroused by movement, their cooperation was readily elicited, and an excellent series of roentgenograms was obtained in both instances. Of 21 children in whom anesthesia was induced by ether, only 1 reacted to the injection, and

9. The Certified Laboratories Products, Ltd., of San Francisco, contributed the tank of ethylene and valve used in this study.

this child became quiet and relaxed toward the end of the injection. The use of tribromethanol in amylene hydrate (90 mg. per kilogram of body weight being given for adults, and up to 100 mg. for children) produced a more variable narcosis. Supplementary inhalation anesthesia, usually ether, was required in 5 of the 62 adults and in 7 of the 15 children. Of 57 adults in whom tribromethanol in amylene hydrate alone was used, 39 were quiet and 18 reacted to the injection. Eleven of the 18 who reacted to the injection were definitely more quiet and relaxed toward the end of the injection than earlier, an effect in contrast to that ordinarily observed with air. Similarly, of 8 children receiving tribromethanol in amylene hydrate alone, 4 showed a reaction

TABLE 2.—*Analysis of the Roentgenographic Results*

	Encephalographic Diagnosis												
Clinical Diagnosis	Internal Hydrocephalus	Cortical Scar	Arachnoidal Adhesions	Asymmetry of Subarachnoidal Spaces	Aplasia or Atrophy	Tumor	Porencephalic Cyst	Total Positive	Normal	No Diagnosis; Unsatisfactory Filling	Total Cases		
Suspected tumor of the brain.	1	..	1	4	3	10	..	13	4	5	22		
Convulsive state (idiopathic).	3	..	2	2	5	9	20	2	31		
Convulsive state (traumatic).	1	4	3	1	1	..	5	13	3	12	18		
Mental defective.....	1	1	3	1	5		
Cerebral arteriosclerosis....	2	1	3		
Encephalitis...	1	1	1	..	2		
Posttraumatic head syndrome	3	3	1	1	5		
Degenerative diseases, central nervous system.....	1	3	3	..	1	4		
Cerebral aplasia or atrophy.	1	4	4	1	..	5		
Psychoneuroses.	2	1	3		
Narcolepsy.....	1	..	1		
Toxic labyrinthitis and polyneuritis	1	..	1		
Totals .	5	4	6	16	25	10	5	47	39	14	100		

to the injection. All 4 were quieter and more relaxed toward the end of the injection than earlier. Although this delayed narcotic effect of the ethylene is not adequate to overcome the immediate acute reaction of the encephalographic injection, it does materially lessen it.

After encephalography with ethylene, headache of slight to moderate severity was usually observed the same afternoon and evening, with slight headache persisting with sitting up and movement for about thirty hours. As with encephalography with air, there is a wide range of individual variation; in general, the reaction of children is less severe and prolonged than that of adults. Whereas 25 of the 64 adults had moderately severe headache, only 5 of the 36 children had a comparable degree of discomfort. Thirty-seven adults and 26 children had mild headache. The remaining 2 adults and 5 children apparently had little or no headache. Thus approximately 85 per cent of the children and

65 per cent of the adults, or 70 per cent of all patients, had mild headache only. This same impression is borne out by a study of the number of patients who required sedatives after encephalography. Twenty-nine of the children received no treatment, and 7 required an average of 2 doses of sedatives, usually codeine (0.015 Gm.) with acetylsalicylic acid (0.3 Gm.). Sixteen of the adults required no sedatives, and, of the remaining 48, 28 received an average of 2 doses of sedative, while 20 required 5, 6 or more doses, usually codeine (0.03 Gm.) and acetylsalicylic acid (0.3 Gm.).

Nausea ordinarily lasted from five to seven hours. Twenty-three of the 36 children vomited, and of these, 2 of 3 (66 per cent) did so only once or twice—a degree of reaction commonly seen following etherization in children. Only 26 of the 64 adults vomited; over one half of these vomited once and three fourths only once or twice. Fluids by mouth were usually tolerated after seven hours, which made hypodermoclysis unnecessary. A soft or regular diet was usually tolerated the following morning, i. e., approximately twenty-two hours after the injection.

The temperature reaction to the injections reached a peak in an average of nine hours and with few exceptions returned to normal in the course of the following morning. The average temperature reaction in adults was 37.9 C. (100.2 F., orally) and in children 38.5 C. (101.3 F., rectally).

The pulse and respiratory rates were retarded slightly in only 6 patients after the injection of ethylene. Follow-up studies of the cerebrospinal fluid, such as those done in the experimental work previously reported,^{1b} were, of course, impossible in this study. In the few instances, however, in which subsequent lumbar puncture afforded an opportunity of studying the cytologic reaction to the injection of ethylene, the results were consistent with those reported in the experimental study and suggested that the cytologic reaction to encephalography with ethylene is not unusual and probably depends more on the amount of gas successfully injected than on the type of gas.

The variation of reactions among the patients with the various clinical conditions in this series is of interest. As a group, the patients suspected of having a tumor of the brain experienced the most difficulty, as might be expected. Although these patients had relatively low grade pressures, as determined by preliminary lumbar punctures in the horizontal position without anesthesia, the reactions tended to be moderately severe and prolonged. Headache persisted for an average of forty-four hours and nausea for fifteen hours. The patients with the syndrome following head trauma also tended to have more severe and prolonged reactions than the average. Those with posttraumatic con-

vulsive disorders usually had slight reactions, but on the average they were prolonged some thirty-four hours. Encephalography was performed on 3 psychoneurotic patients in order to rule out organic lesions. These appeared especially sensitive to the procedure, and their subjective complaints continued considerably longer than the average. The patients with the other conditions as a rule had slight reactions.

In general, 80 per cent had mild reactions, while 20 per cent had moderately severe reactions. Of those patients having a mild reaction, the discomfort was prolonged beyond thirty hours in only 10. On the other hand, 14 of the 20 patients who experienced moderately severe reactions were distressed beyond the average thirty-hour period. Two of the reactions were exceptionally prolonged and simulated a subacute, sterile meningitis. Aside from these 2, only 6 approximated in severity and duration the usual reaction after encephalography with air.

The roentgenographic series was readily obtained for 93 of the 100 patients. The series was obtained with some difficulty and delay in the case of 3 children, and ether was administered to the remaining 4 patients (2 children and 2 adults) to insure satisfactory roentgenographic results. Tribromethanol in amylene hydrate had been given previously to 3 of these patients. The average period required for taking the roentgenograms was forty minutes, and an average of fifty minutes elapsed from the completion of the injection to the completion of the x-ray series. Although this time could be reduced, as already explained, the slower technic was insisted on in this study to settle beyond question the practicability of the gas from the roentgenographic standpoint. Excellent roentgenograms were obtained in 42 cases; 33 of the roentgenograms showed good filling and 11 fair filling, while the results in 14 were unsatisfactory. It should be emphasized that the best roentgenographic results were obtained in the first half-hour after the injection. The poor results were almost invariably due to encephalographic injections which were only partially successful and delayed beyond this period or to a delay beyond forty or fifty minutes in the case of more adequate injections.

An analysis of the roentgenographic results is presented in table 2. The clinical and roentgenographic diagnoses are listed with the number of cases in which the diagnoses were made.

Of 22 patients who were suspected of having tumor of the brain, 13 showed definite roentgenographic findings suggesting pathologic changes and 4 showed pictures considered to be normal. A diagnosis of tumor was made in 10 cases. Satisfactory encephalograms were not obtained in 5 instances. Subsequent operation in 1 of these cases revealed a tumor of the brain, and autopsy in a second revealed an abscess

of the brain. Ventriculograms were made in the other 3 cases. Satisfactory fillings were obtained in 2 of these 3, and in both a diagnosis of tumor was made.

Of 31 patients with a clinical diagnosis of a convulsive state of unknown origin, 9 showed positive roentgenographic findings; 20 normal findings and 2 inadequate filling.

Of 18 patients in whom a convulsive state of posttraumatic origin was diagnosed, 13 showed positive roentgenographic findings and 3 a normal roentgenographic picture, and 2 inadequate filling.

If the instances of inadequate filling are deducted from the foregoing figures, to correspond with the analysis presented in the study of encephalography with air by Stone and Jones,⁷ it will be seen that the results are comparable. Stone and Jones reported 14 cases in which filling was unsatisfactory in addition to the 113 cases which formed the basis of their analysis. The ventricles were not demonstrated in 7 of the 113 cases. Thus, of a series of 127 cases in which encephalography with air was done, failure to obtain satisfactory ventricular filling occurred in 21, and failure from the standpoint of visualization of the subarachnoid spaces in 14. In the series of 100 cases in which encephalography was done with ethylene, inadequate ventricular filling occurred in 14, and the subarachnoid filling was unsatisfactory in 11. Demonstration of the subarachnoid spaces in 89 cases showed abnormal results in 38, while in the remaining 51 the results were within normal limits. These results are comparable to those obtained with the use of air as reported by Stone and Jones.

Since the specific gravity of ethylene is almost identical with that of air, and its solubility is such that good roentgenographic results may be obtained when filling is satisfactory, up to one hour, the comparable results obtained with these gases might have been expected. It should be stated, however, that, while the ventricular fillings with ethylene were fully as good as the results obtained with air and the diagnostic demonstration of the subarachnoid spaces was comparable for both gases, the filling of the subarachnoid spaces with ethylene was appreciably less massive than with the use of air. Correspondingly, the large cortical "lakes" of gas, "superfluitant" gas and sagging of the brain observed by Stone and Jones⁷ in their follow-up studies on encephalography with air did not occur in this series. Such findings are probably best explained by the prolonged presence of the air. Approximately 79 per cent of air is composed of nitrogen and other even more insoluble gases. The rate of absorption of ethylene, as determined by the estimated rate of disappearance of the gas in repeated follow-up roentgenograms, is shown in figure 2.

It is perhaps worthy of mention that 5 patients have been strikingly relieved of their symptoms after this procedure. Two patients with a syndrome following head trauma and 3 with convulsive states of the idiopathic type have reported relief following encephalography with ethylene.

COMMENT

There is an obvious difference between the duration and severity of the reactions obtained in encephalography with the use of nitrous oxide and ethylene and those in encephalography with the use of air (table 1).

The sedative effect of the anesthetic gases in children insured a satisfactory procedure throughout and necessitated only an initial induction of anesthesia. In adults, when the narcotic effect of the tribromethanol in amylene hydrate was so slight that the initial injection of gas aroused them, the sedative effect of the gas usually resulted in the patient's being more quiet and relaxed through the latter part of the injection and during the period of roentgenography than at the start. This effect was in striking contrast to the usual effect and course of an injection of air under light anesthesia. Thus, in both adults and children the sedative action of the anesthetic gases tended to lessen the severity of the immediate reaction and materially assisted in making the procedure easier and the results more satisfactory.

The rapid absorption of the anesthetic gases, on the other hand, resulted in shortening the reaction after encephalography. Specifically, the period of headache, nausea and malaise was reduced from about three days to one day. Fluids were tolerated the same afternoon or evening, and hypodermoclysis and intravenous therapy usually were not required. A good proportion of the patients did not require sedatives, and the majority of those who did needed them but once or twice. Hospitalization was correspondingly reduced. The economic saving involved is obvious.

The shortened and lessened reaction associated with the use of anesthetic gases in encephalography may justly be considered as a factor of safety in certain instances. A few patients suspected of having a tumor of the brain, with a low degree of increased intracranial pressure, have weathered the reaction to encephalography with ethylene in such a way as could not reasonably have been expected had air been used. Among 14 patients with a diagnosis of tumor of the brain in the series of 100 in which ethylene was used, operation was forced only once. In this connection, it should be added that the accentuation of symptoms and alteration of signs noted by Cairns¹⁰ after injections of air are

10. Cairns, Hugh: Observations on the Localization of Intracranial Tumors. *Arch. Surg.* 18:1936-1944 (April) 1920.

usually less marked or are absent after encephalography with the use of ethylene.

As a point of comparative interest, it is perhaps worthy of mention that 4 patients in the series of 100 in whom ethylene was used had previously undergone encephalography with air at other institutions. The enthusiastic testimony of these patients has emphasized, from a subjective standpoint, the difference in reaction, observed clinically after encephalography. One of these patients, indeed, would not believe at first that the procedure had been repeated on him.

Of the two anesthetic gases, ethylene is the more practical. The absorption of nitrous oxide is so rapid that good roentgenographic results cannot be ensured without considerably reducing the period required for taking the films. Undue haste in the roentgenographic technic in many cases undoubtedly would prove to be a distinct disadvantage. This is the limiting factor in the practicability of nitrous oxide.

Three points in the practical aspect of encephalography with ethylene are worthy of emphasis. First, pure ethylene is not explosive, and the danger of the oxygen-ethylene mixture as used for inhalation anesthesia does not exist. The danger of an explosive mixture being formed, with the escape of ethylene into the room on the filling of the bag and initial forcing of air out of the tubing, is negligible, provided large amounts of the gas are not allowed to escape in the presence of lighted matches, cigarets, etc. With ordinary care, the procedure should be entirely safe.

Second, the equipment needed is simple and inexpensive. A small tank of ethylene with a valve may be bought or inexpensively rented from any reliable company handling anesthetic gases. One tank should be adequate for hundreds of injections.

Third, the use of the equipment, according to the method mentioned, is simple and requires little more time than the injection of air. Simple modifications of this technic and the adaptation of other methods to the use of ethylene will readily occur to those interested.

CONCLUSIONS

1. Nitrous oxide and ethylene are safe agents for use in encephalography. Their action is relatively nonirritating and is not associated with bad after-effects.

2. Good roentgenographic results may be obtained with both gases, but the slower disappearance of ethylene makes it more practical for ordinary use. With a good ventricular filling, satisfactory views may be obtained for approximately forty or fifty minutes after the injection.

3. The slight, but definite, sedative effect of ethylene lessens the severity of the immediate reaction to encephalography and materially assists in making the procedure easier and the results more satisfactory. In children the induction of anesthesia alone is required, the sedative effect being sufficient to carry them through the remainder of the procedure.

4. The relatively rapid rate of absorption of ethylene results in a marked shortening of the reaction. The period of headache, nausea and malaise is reduced from about three days, as in the case of air or oxygen, to approximately thirty hours, with a corresponding reduction in hospitalization. Supportive treatment is either not required or is required only to a limited extent.

5. The simplicity of the equipment and technic necessary for the *encephalographic injection of ethylene* makes the procedure entirely practicable. Within a closed system the pure gas is not explosive and can be used with safety in any of the various methods of encephalography.

CONGENITAL ATRESIA OF THE PELVIC COLON

REPORT OF A CASE

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AND

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MINNEAPOLIS

A case of congenital atresia of the sigmoid colon is reported not only because of the rarity of the condition but because the case illustrates certain points to be observed in the diagnosis of gastro-intestinal conditions in the new-born.

REPORT OF CASE

S., a boy, entered the University Hospital forty-eight hours after a spontaneous delivery with breech presentation after a labor of eight and one-half hours. No meconium was passed during delivery or at any time subsequently, although urine was voided normally. The weight at birth was 6 pounds and 13 ounces (2,996 Gm.). Moderate difficulty was experienced in initiating respiration, and during the first day the legs, hands and face repeatedly became cyanotic. Respirations were shallow and feeble. The infant vomited twice during the first day and then regurgitated frequently during the second day.

Physical examination showed a markedly icteric infant with cyanotic hands and feet. The abdomen was distended, but no masses were palpable. The anus was present, but the canal ended in a blind pouch at a depth of about 6 cm. Laboratory findings included normal urine and 7,700 leukocytes per cubic millimeter of blood.

Roentgen studies showed marked gaseous distention of the stomach and several loops of small bowel (fig. 1A). A small amount of barium sulfate was given by stomach tube and was seen in the small intestine in a few hours. The distended loops could not be identified definitely. With the infant in the inverted position and with a thermometer in the anal canal, films showed a canal about 5 cm. in length, seemingly separated from the dilated bowel by a relatively thin partition (fig. 1B).

Within a few hours after his admission to the hospital the infant was operated on by Dr. M. H. Manson, ether anesthesia being used. The buttocks and anus were prepared with tincture of merthiolate, and a Kelly cystoscope was introduced into the rectum, which appeared to be normal. It was lined by normal mucous membrane extending from the anal margin for a distance of about 5 cm. At this point visualization was good, and there appeared to be only a blind pouch with a small dark spot at the apex. An alligator forceps was introduced through the cystoscope. Gentle pressure was exerted at the end of the cul-de-sac, but no tear and no escape of gas resulted. Then, with a no. 15 Bard-Parker knife, a tiny nick was made in the end of the cul-de-sac, with a similar result. The hole was explored with the end of an applicator, and the impression formed was that the probe had gone through the pelvic peritoneum. It was not determined whether the large or the small bowel was visualized through the aperture. Because of the

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high position and the uncertainty of what structures were present, it was decided that further manipulation posteriorly was not advisable. There was already a moderate amount of trauma but little bleeding. The infant was returned to the ward and was given saline solution subcutaneously, after which he was returned to the operating room, where the abdomen was prepared with tincture of merthiolate, and the peritoneal cavity was entered on the left side through a McBurney incision, local anesthesia being used. There was a considerable amount of bloody fluid present, which probably came from the manipulation below. A distended loop of bowel presented itself in the wound. This loop resembled colon and was covered by a thin layer of adhesions. No communication between this loop and the large bowel could be demonstrated, and after careful exploration the left lower quadrant, the left lateral gutter and the pelvis were found to be entirely free from any structure resembling bowel. A small urethral catheter was sewed into the

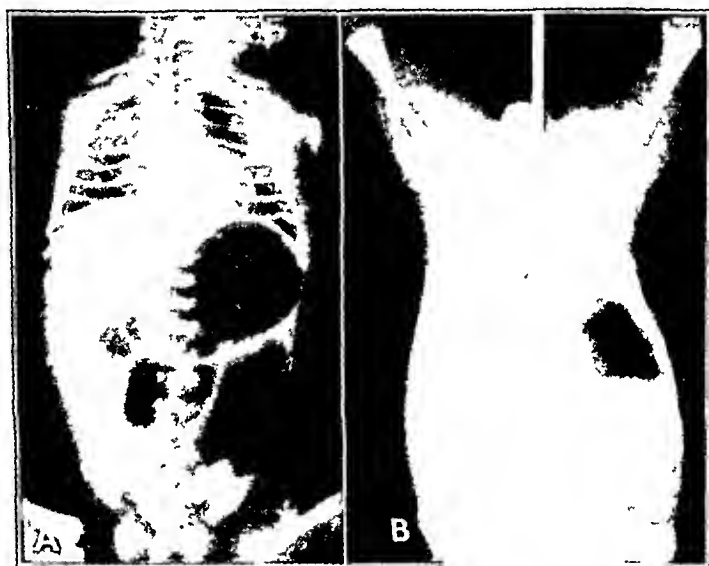


Fig. 1.—*A*, a roentgenogram showing gaseous distention of the stomach and the small bowel. *B*, a roentgenogram taken with the infant in the inverted position and with a thermometer in the anal canal.

dilated bowel, and the abdomen was closed. The infant's condition became progressively worse, and death occurred on the third postoperative day.

The only significant observation at autopsy concerned the intestinal tract. The esophagus and stomach showed no change. The pyloric ring was palpated in its normal position and relation. The entire duodenum was thick walled and extremely dilated, being 3 cm. wide in the collapsed state. There was an angulation at the duodenojejunal junction, but the dilatation and thickening extended about 24 cm. down the jejunum. The enterostomy had been performed at the middle of this jejunal loop. This segment was on the left side of the abdomen, extending down to the position usually occupied by the sigmoid colon. At the pelvis it turned upward again and ended in a mass made up of loops of intestine held firmly together by mesentery and heavy adhesions. The loops were separated by sharp dissection, and three sharp angulations were demonstrated in the mass. The dilatation of the small bowel ended abruptly at this mass, and distally the caliber of

the bowel was normal. It was collapsed through most of its extent but contained small masses of meconium. The cecum lay under the liver and contained meconium. The transverse and the descending colon were normal in position and relation, being small and collapsed. The colon ended abruptly at the brim of the pelvis and distally there was a cord extending to the floor of the pelvis and uniting with the anal canal. The anal canal was normal (fig. 2).



Fig. 2.—Gross specimen showing the marked dilatation of the duodenum and jejunum with the enterostomy tube in place. The angulations in the jejunum and ileum have been freed by dissection. The fibrous cord representing the sigmoid colon is shown connecting the descending colon and the anal canal.

COMMENT

Farr and Brunkow¹ in 1925 stated that the usual incidence of atresia of the intestinal canal is 1 in 20,000 births. Of these, by far the majority are located in the duodenum, about 1 in 10 being found in the colon. Davis and Poynter reviewed all reported cases up to 1922 and found 401 instances of atresia, of which 39 were in the colon.

1. Farr, G. E., and Brunkow, C. W.: Congenital Abnormalities of the Intestine, *Arch. Surg.* **11**:417-434 (Sept.) 1925.

Congenital atresia is divided into three types by Forssner, according to Andreassi.^{1a} First, there may be a complete or an incomplete mucosal membrane interrupting the intestinal lumen. Second, there may be a solid cord connecting the proximal and distal segments. This is made up of serosa, muscularis and submucosa. There may be a complete epithelial lining, scattered epithelial cells or total absence of epithelial elements. Third, there may be two separate segments of intestine, either contiguous or at a distance.

The theories as to causation have been well explained by Cole² and by Heckel and Apfelbach.³ 1. Tandler and Kreuter found the original lumen of the gastro-intestinal tract of most vertebrates to be lost in early embryonic life by epithelial proliferation and later reestablished. They assumed that there was a failure of recanalization. 2. Bland Sutton maintained that atresia occurs at the site of embryonic events, as at the junction of the rectum and anus or at the ampulla of Vater. 3. Vascular disturbances resulting from vascular anomalies, embolism or thrombosis of the mesenteric vessels or intra-uterine twisting of the intestine may be of importance. 4. Defective intestinal rotation has been suggested as an etiologic factor. 5. Chiari mentioned healed intussusception as a cause of atresia. 6. Miscellaneous factors, such as fetal peritonitis, volvulus and syphilis, have also been suggested.

In cases of congenital atresia, the history is most valuable in diagnosis. The important points are vomiting and absence or abnormality of the meconium. Early appearance and severity of vomiting are in direct proportion to the level of atresia. Absence of meconium indicates a relatively low obstruction, and absence of bile pigments places the lesion below the ampulla or else indicates a pathologic process of the bile duct. As Farber⁴ and Ladd^{4a} indicated, the presence of amniotic fluid in the meconium is of great importance. Atresia occurs before vernix, lanugo and cornified squamous cells develop, and their absence in the meconium therefore is evidence of atresia. Vomiting of amniotic fluid is usually pathognomonic. In imperforation of the anal canal and rectum, Wangenstein and Rice⁵ advocated roentgen examination of the

1a. Andreassi, G.: Considerazioni intorno a un caso di atresia congenita del colon ileo-pelvico, *Ricerche di morfol.* **11**:375-383, 1931.

2. Cole, W. H.: Congenital Malformations of the Intestinal Tract, *Arch. Surg.* **23**:820-848 (Nov.) 1931.

3. Heckel, N. J., and Apfelbach, C. W.: Congenital Atresia of the Colon, *Am. J. Dis. Child.* **34**:1050-1056 (Dec.) 1927.

4. Farber, S.: Congenital Atresia of the Alimentary Tract: Diagnosis by Microscopic Examination of Meconium, *J. A. M. A.* **100**:1753-1754 (June 3) 1933.

4a. Ladd, W. E.: Congenital Obstruction of the Small Intestine, *J. A. M. A.* **101**:1453-1458 (Nov. 4) 1933.

5. Wangenstein, O. H., and Rice, C. O.: Imperforate Anus—Method of Determining Surgical Approach, *Ann. Surg.* **92**:77-81, 1930.

infant in the inverted position, with an opaque disk over the anal plate. Observation of the degree of proximity of the gas bubble in the bowel and the opaque object at the anus will often give valuable data concerning the feasibility of an operative attack (fig. 3). In the case reported here, the three partially obstructed areas in the jejunum in addition to the atresia made a corrective surgical operation too formidable. In reconstructing the details of the case with the roentgen and postmortem observations in mind, it is obvious that the preoperative impression of simple atresia of a small area in the upper portion of the rectum was not well founded. The distention of the stomach and upper reaches



Fig. 3.—Roentgenogram, in the inverted posture, of an infant with imperforation of the anal canal and rectum. The similarity to figure 1*B* is apparent, but in this film the opaque object (shot) rests on the anal plate. In figure 1*B* the thermometer could be introduced into the extrapelvic reaches of the bowel.

of the small intestine, as indicated in figure 1 *A*, indicates clearly that there was an obstruction of the small intestine. As a matter of fact, this was the chief cause of the clinical obstruction, as shown by the segments of distended intestine and as corroborated by necropsy. The small bowel beyond the site at which the mass of adhesions had obstructed the intestine was collapsed, as was the colon. Had the atresia of the pelvic colon been the only obstruction present, the configuration of the distended bowel would have been in the nature of a horse-shoe curve in conformity with the extent of the colon. The distention in such instances is also usually limited to the colon, particularly in obstruc-

tion of the pelvic colon in adults due to carcinoma. As Wangensteen⁶ pointed out, vomiting may be absent. The competent ileocecal sphincter limits the distention to the colon by precluding regurgitation of colonic content back into the ileum. In infants with imperforation of the anal canal and rectum, however, unlike adults with acute obstruction of the colon on the left side, vomiting is the rule, despite the fact that the distention usually concerns only the colon.

The contrast apparent between figure 1 *B* and figure 3 sets fairly definitely aside the thought that this lesion might be due to atresia of the upper portion of the rectum. Imperforation of the rectum, as Keith⁷ pointed out, concerns essentially the postallantoic intestine. The part of the hindgut which goes to form the rectum is rarely if ever involved in imperforation. In this instance, on the contrary, that portion of the anal canal and rectum which are usually concerned had a lumen, and the atresic area involved the bowel above.

The difficulty of operating on an infant with obstruction of the bowel is a matter of common knowledge. In the case reported here the pathologist had a difficult time unraveling the ensnarled bowel at necropsy. At operation it was believed that the catheter had been inserted into the pelvic colon. The correct operative procedure would have been disentanglement of the obstructed small bowel from the adhesive bands and colostomy proximal to the site of atresia. The newborn infant notably stands enterostomy poorly. In our experience, all infants with congenital atresia of the small intestine on whom enterostomy has been performed have died. About a dozen have survived when an entero-anastomosis was established between the proximal distended segment and the distal collapsed segment (Wangensteen⁸).

It is unlikely in the instance here reported that even if the exact nature of these two obstructions had been precisely identified the infant could have tolerated the corrective procedures necessary to afford adequate relief.

SUMMARY

A case is reported of congenital atresia of the pelvic colon, complicated by an additional obstruction of the small intestine. The criteria which set this unusual form of intestinal atresia aside from imperforation of the rectum are discussed.

6. Wangensteen, O. H.: Vomiting and Distention in Intestinal Obstruction, *Journal-Lancet* 54:640-645, 1934.

7. Keith, A.: Malformations of the Hind End of the Body, *Brit M J* 2:1736-1741, 1908.

8. Wangensteen, O. H.: Personal communication to the author.

OPERATION ROOM INFECTIONS

CONTROL OF AIR-BORNE PATHOGENIC ORGANISMS, WITH PARTICULAR
REFERENCE TO THE USE OF SPECIAL BACTERICIDAL
RADIANT ENERGY; PRELIMINARY REPORT

DERYL HART, M.D.

DURHAM, N. C.

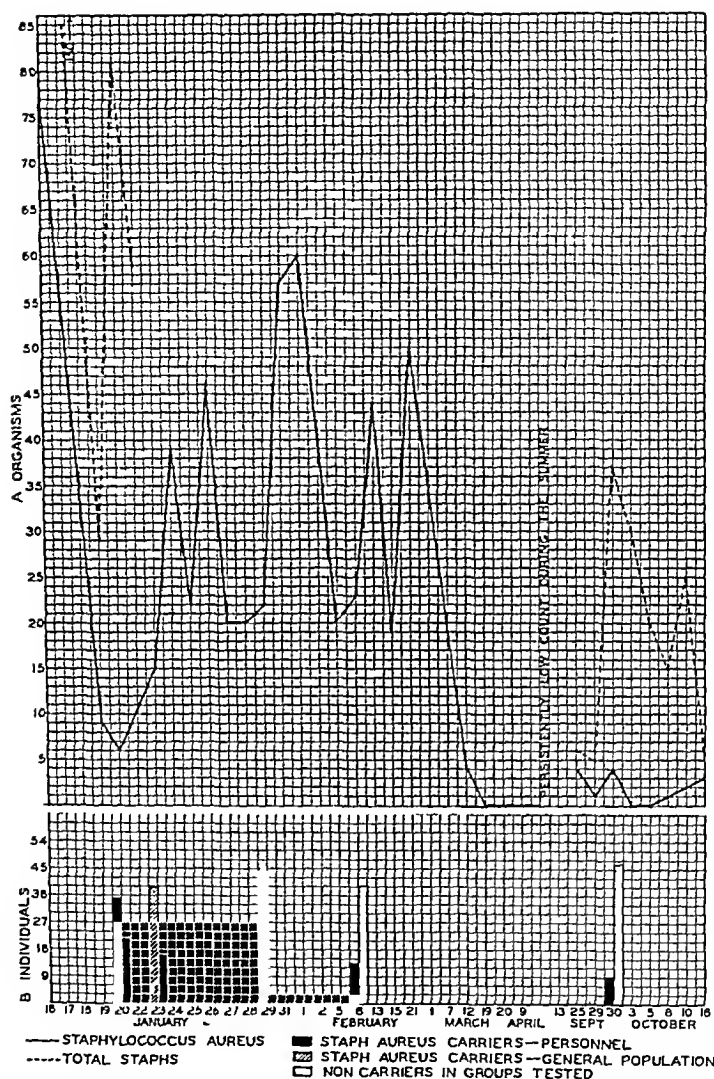
During the past five years my co-workers and I have been making a concerted effort to control the occasional sporadic operating room infection occurring in a case of otherwise clean operation. About 90 per cent of the infections have been caused by *Staphylococcus aureus*, usually of the hemolytic type. Occasionally there has been a mild infection with *Staphylococcus albus* and rarely a severe infection with *Streptococcus haemolyticus*.

Beginning with the cleansing of the skin of the patient, the operating room technic was checked throughout. This survey covered the skin of the operative field, the hands of the operating team, the linen used for draping, sponges, autoclaves, sterile water tanks, hot water sterilizers, oil sterilizers, brushes, instruments, gloves, plain and chromic catgut, needles, silk, scalpels and solutions and powder for the hands and gloves. Cultures of these were uniformly found to be sterile. Freshly laundered doctors', nurses' and orderlies' uniforms and blankets and sheets were found to be free from pathogenic bacteria. The shoes worn in the operating room were free from *Staph. aureus-haemolyticus*, which was responsible for most of the infections.

Cultures of the walls, floors and ceilings of the operating rooms showed an occasional *Staph. aureus-haemolyticus*. The celotex ceiling in the corridors outside the operating rooms showed large numbers of organisms, both pathogenic and nonpathogenic. Plates of sterile blood agar exposed to the air in all operating rooms for one hour and cultured for from twenty-four to forty-eight hours (fig. 1) showed as high as 78 colonies of *Staph. aureus*, while the total number of colonies of all organisms at times was as high as 150 (fig. 1A).

This work was done in an attempt to solve our local problem and without a complete survey of the literature. Since we became interested in this question the literature has been reviewed, and we are familiar

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with the work of Meleney,¹ Dandy,² Brewer,³ Goff,⁴ Whipple,⁵ Davis,⁶ Hunt⁷ and others. We do not claim originality in much of this work, and refer the reader to the articles cited. We feel strongly, however, that pathogenic organisms in the air contaminated by human beings are responsible for most of our operating room infections. This point, while referred to, has not been sufficiently emphasized; it is placed secondary to contamination of the skin and is not generally considered to be of major importance. The problem of proper masking is referred to in a number of articles, such as those of Davis,⁶ Meleney,¹ Walker,⁸ Whipple,⁵ Doust and Lyon,⁹ Kellogg and MacMillan,¹⁰ Blatt and Dale,¹¹ Leete,¹² Capps,¹³ Dannenberg,¹⁴ Mellinger¹⁵ and Weaver.¹⁶ These

1. Meleney, F. L.: Infection in Clean Wounds, *Surg., Gynec. & Obst.* **60**: 264-276, 1935; Seasonal Incidence of Hemolytic Streptococcus in Nose and Throat, *J. A. M. A.* **88**:1392-1394 (April 30) 1927. Meleney, F. L., and Stevens, F. A.: Postoperative Hemolytic Streptococcus Wound Infections and Their Relation to Hemolytic Streptococcus Carriers Among Their Operating Personnel, *Surg., Gynec. & Obst.* **43**:338-342, 1926.

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3. Brewer, G. E.: Studies in Aseptic Technique, *J. A. M. A.* **64**:1369-1372 (April 24) 1915.

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9. Doust, B. C., and Lyon, A. B.: Face Mask Infections of the Respiratory Tract, *J. A. M. A.* **71**:1216-1219 (Oct. 12) 1918.

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11. Blatt, Maurice L., and Dale, M. L.: A Bacteriological Study of the Efficiency of Face Masks, *Surg., Gynec. & Obst.* **57**:363-368, 1933.

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13. Capps, J. A.: Measures for the Prevention and Control of Respiratory Infections in Military Camps, *J. A. M. A.* **71**:448-451 (Aug. 10) 1918.

14. Dannenberg, A. M.: A Simple Face Mask for Use by Contagious Disease Attendants, *J. A. M. A.* **70**:990 (April 6) 1918.

15. Mellinger, H. V.: A New Mask That Protects Both Physician and Patient, *J. A. M. A.* **95**:662-663 (Aug. 30) 1930.

16. Weaver, G. H.: The Value of the Face Mask and Other Measures, *J. A. M. A.* **70**:76-78 (Jan. 12) 1918; Droplet Infection and Its Prevention by the Face Mask, *J. Infect. Dis.* **24**:218, 1919.

authors considered the inadequacy of the usual gauze masks, suggested covering the nose and mouth and described new types of masks or a different mesh or thickness. In certain cases there was only a slight reduction in the number of organisms in the air as a result of the suggested change. None of the reports showed that the degree of contamination in the air can be kept as low with human beings present and masked in any way as when they are not present. This, together with the comfort of the wearer, should be the criterion for a satisfactory mask from the point of view of preventing contamination of the air.

The rooms were all repainted, the celotex ceiling was replaced by plaster and walls and floors were washed daily with an antiseptic solution. The incoming air from the forced ventilating system, taken from above

*Result of Cultures of the Air Taken in Various Locations in the Hospital **

Date	Location	Duration of Exposure, Hr.	Staphylococcus	
			Aureus	Albus
January 19	Accident room	1	0	3
19	Corridor of medical school	1	0	5
19	Autopsy room	1	0	9
19	N. & T. office	1	8	18
19	N. & T. examination room	1	8	7
20	Observation room, students present	1	12	60
20	Sterilizing room	1	1	30
20	Delivery room no. 1	1	0	2
20	Delivery room no. 2	1	0	3
20	Gynec. examining room	1	0	6
21	Instrument room	1	0	0
21	Ventilator duct	1	0	0

* The cultures were made by exposure of blood agar plates in various rooms throughout the hospital and medical school at a time when the bacterial contamination in the operation room was very high (see graph in figure 1 for the air contamination during January). The number of colonies per plate varied with the number of persons and the duration of occupancy. All of the exposures except those made in the examining room and office (N. & T.) used for patients with diseases of the nose and throat, the sterilizing room and the observation room were made when the rooms were unoccupied. These cultures, together with those illustrated in figures 1 to 7, made us feel that the degree of air contamination was dependent on the number of carriers, the degree of infection of their noses and throats and the duration of occupancy.

the roof and washed, was found to be practically free from pathogenic bacteria. Only rarely was a single colony of *Staph. albus* present on a plate exposed for one hour (fig. 2). It was thought that this might have been brought back from the highly contaminated air in the operating room (fig. 3) to the duct outlet by eddies in the air current.

Cultures of the air taken while the room was unoccupied and with the air agitated with electric fans showed far fewer organisms than were present in cultures taken when the room was occupied and as quiet as possible (fig. 4). It was then found that at times the noses and throats of from 60 to 80 per cent of the operating room personnel contained *Staph. aureus*, frequently of the hemolytic type (fig. 1 B). The same condition was found in a group of persons taken at random from the population outside the hospital (fig. 1 B). On any date the number of organisms falling out of the air within a given time varied

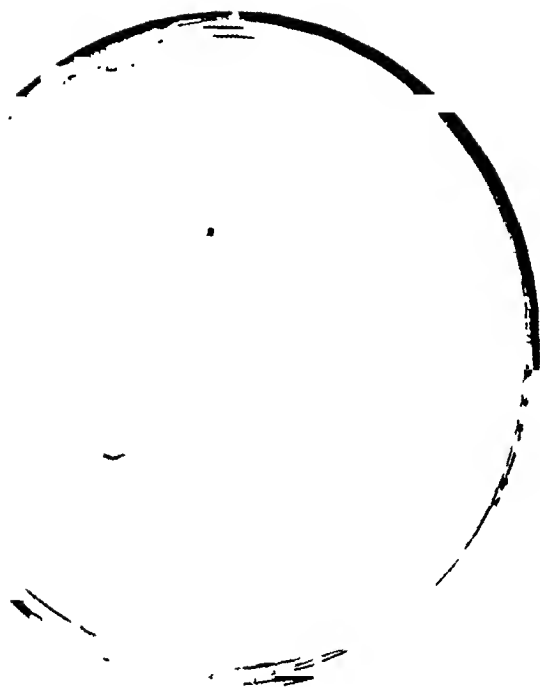


Fig. 2.—Petri dish of blood agar exposed for one hour to the clean washed air which was used to ventilate the operating rooms. Most of these cultures showed no growth, but on an occasional plate there were one or two colonies of *Staph. albus*. These may have reached the plate from the contaminated air of the room (fig. 3).

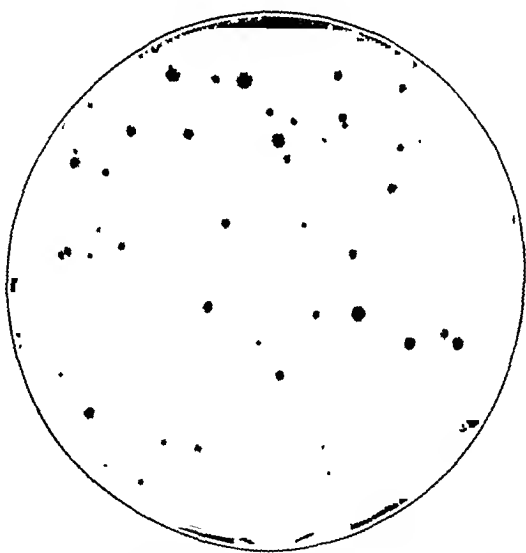


Fig. 3.—A typical forty-eight hour culture of a sterile Petri dish of blood agar exposed to the air of the operating rooms for one hour during an operation at a time of relatively high bacterial contamination of the air. The colonies were identified as follows: *Staph. aureus-haemolyticus*, 6; *Staph. aureus*, 6, and *Staph. albus*, 32. Even though the usual operations with small incisions can be performed with little risk of infection, we have found that at such a time it is quite dangerous to perform operations of the magnitude of a thoracoplasty or radical amputation of the breast.

directly with the number of persons present and the duration of occupancy (see figure 4 and compare figure 1 with the table). The air of the autopsy room, bacteriologic laboratory, private examining rooms for persons with diseases of the nose and throat and other places throughout the hospital not occupied by a considerable number of persons (table) was less contaminated than the air of the operating rooms. This confirmed our impression that the amount of contamination was determined by the number of persons present and the duration of occupancy. The degree of contamination also varied in the same room under similar conditions at different times of the year, depending on the percentage of persons who were carriers at that time and the intensity of the growth in the noses and throats of the carriers (fig. 1).

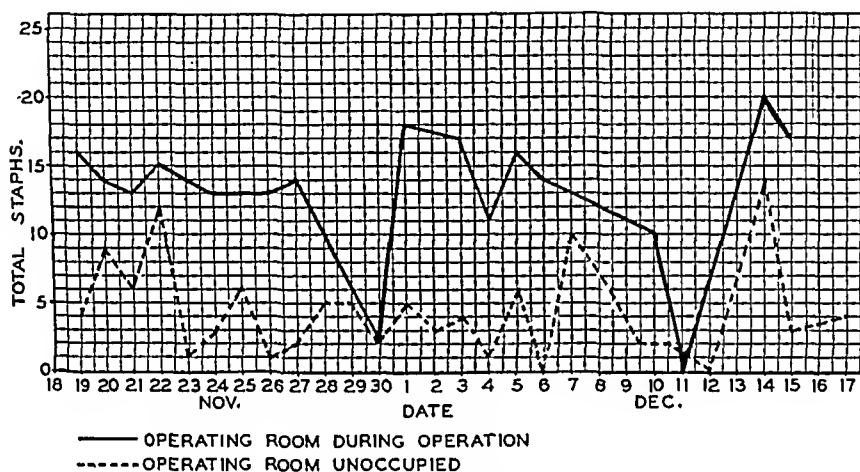


Fig. 4.—Graph showing that the contamination of the air was much less when the room was unoccupied than when it was occupied. A comparison with the table shows also that the rooms occupied only occasionally for only a short time had still fewer organisms in the air. These graphs also show that even though the number of organisms was greatly reduced (compare with figure 1) we were unable to free the air from pathogenic bacteria.

Rigid censorship was placed on a group of three operating rooms. No visitors were allowed; every one entering, including the patients, wore heavy masks over the nose and mouth at all times. No person with an infection of the nose and throat was treated in these rooms, and two masks were worn during all major operations.

An attempt was made to identify all carriers of hemolytic staphylococci, and these persons were not allowed in the operating rooms. It was found, however, that cultures of material from the nose and throat varied from positive to negative from day to day, so that this was impracticable. However, all persons with heavy, persistent infections

of the nose and throat with *Staph. aureus*-haemolyticus were kept out and treated with bacteriophage and autogenous vaccines until they were free from the organisms. This quarantine and other precautions reduced but did not completely eliminate the contamination of the air with

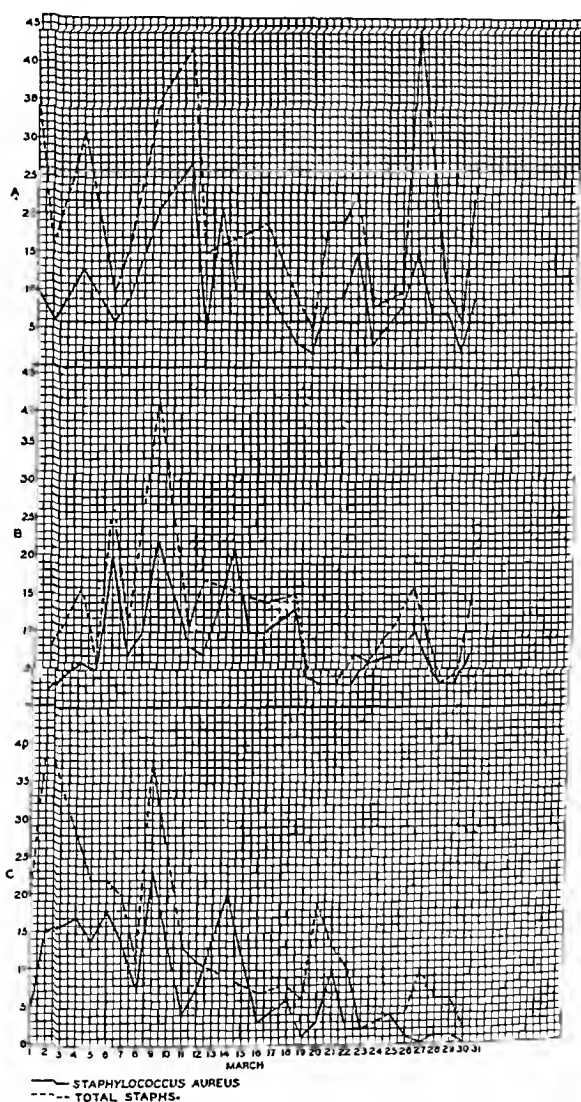


Fig. 5.—In spite of all precautions there were still peaks of air contamination, at which times the danger of infection in wounds with a large exposed area was great. These peaks were most pronounced during epidemics of infection of the respiratory tract, particularly those occurring during the winter. At such times the same organisms were present in the noses and throats of a large percentage of the operating room personnel (see fig. 1).

hemolytic staphylococci, as shown in figures 5 and 6 (compare figures 5 and 6 with the first part of figure 1). We realize, of course, that other organisms such as streptococci are present at times in the noses

and throats of large numbers of the population and give rise to an epidemic of operating room infections. The surgeon is much more likely to become upset by a streptococcic infection, since the staphylococcic infection is considered to be a contamination from the skin. At most it may incite a change in the preparation of the skin or the scrubbing technic, while the real source of contamination from the air is unsuspected. Any one who doubts the tremendous importance of this contamination from the air need only compare a culture plate exposed to the air for an hour with one inoculated from thoroughly cleaned skin to determine where the greater number of organisms are found.

Double doors were put in so as to prevent currents of air from the wards reaching the operating rooms. The ventilating fans were set

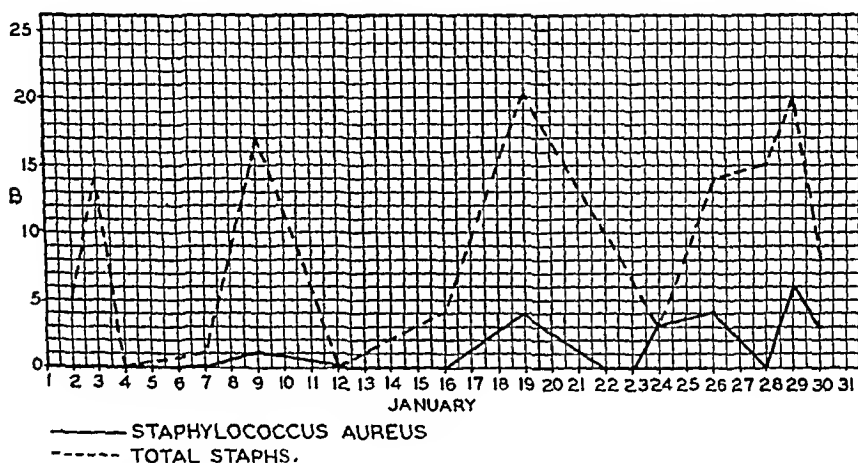


Fig. 6.—Period of low air contamination. At such times there was a relatively low incidence of carriers among the operating room personnel. The contamination in all rooms was correspondingly low.

so that the inflow of clean air (fig. 2) was greater than the outflow, thus forcing a current of air out of all cracks and open doors.

After the institution of these measures there was a marked drop in the degree of contamination of the air (see figures 5 and 6 for periods of high and low contamination and compare with figure 1). There were usually less than 20 colonies in all and less than 5 colonies of *Staph. aureus* per plate after an hour's exposure during an operation (fig. 6). There were, however, still peaks during epidemics of infections of the respiratory tract when the number of organisms in the air was greater (fig. 5). Many will consider that the large number of staphylococci in the air is peculiar to our location. This is definitely not the case, since every report we have seen in the literature (Meleney from New York, Davis from Baltimore, Hunt from New England, etc.)

gives a higher contamination with these organisms than we have had during the past two or three years.

The total bacterial count seemed to us to be of less significance than the degree of contamination with *Staph. aureus*, particularly the hemolytic type. Whenever the *Staph. aureus* count was above 5 colonies per Petri dish exposed for one hour during an operation, we considered that there was danger of an infection occurring in patients on whom an extrapleural thoracoplasty or radical amputation of the breast was performed. In all severe infections which occurred a considerable number of *Staph. aureus-haemolyticus* had been found on the Petri dish of blood agar exposed during the operation. A graph was plotted showing the daily contamination of the air during operations in all rooms, and all operative procedures necessitating the exposure of a large raw surface were postponed until the contamination was found to be low (compare figure 5 with figure 6). In general, the contamination with the more virulent organisms was greater during the winter months than in the summer and fall. There were, however, periods of low contamination in the winter months (compare January in figure 1 with the following January in figure 6). Patients needing a collapse of the chest were always advised to wait until the summer or fall, when the contamination of the air was persistently low (fig. 1) without the peaks of high contamination so frequently seen during the colder months. Only emergency operations of any type were performed during the peaks of infection of the respiratory tract, at which times we found the contamination of the air to be greatest (compare figure 5 with figure 6).

All major operations requiring exposure of a large raw area, as noted previously, were scheduled only when the contamination of the air was at its lowest and then were posted first in the morning before the room had been occupied long. The ventilating fans were run continuously to replace the contaminated air with clean air (fig. 7). At the end of the operation the wounds were thoroughly washed out with several liters of sterile salt solution. In certain cases the wounds were painted with methyl rosaniline (gentian violet) in the hope that it would inhibit growth of staphylococci. Even with these regulations and precautions, an occasional infection occurred in the patients having more extensive operations (fig. 17). *Staph. aureus* could be cultured from the incision or drainage tract in 33 per cent of the cases in which extrapleural thoracoplasty was performed. However, only four patients in a series of over one hundred on whom thoracoplasty was done and only one patient of a large number having a radical amputation of the breast died as a result of the infection. Of those remaining, only a few would have been considered infected either from the gross appearance

of the wound or from the clinical course. We do not feel that the incidence of operating room infections in the Duke Hospital was higher than elsewhere in this country. Since the institution of these precautions it is probably lower than is generally encountered where such precautions are not taken.

BACTERICIDAL IRRADIATION

In further attempting to eliminate completely this grave danger to every patient undergoing a major operation, we turned to irradiation with such wavelengths as are known to kill organisms. We first tried a therapeutic ultraviolet ray lamp and proved that we could kill a sprayed culture of *Staph. aureus-haemolyticus* at a distance of 8 feet

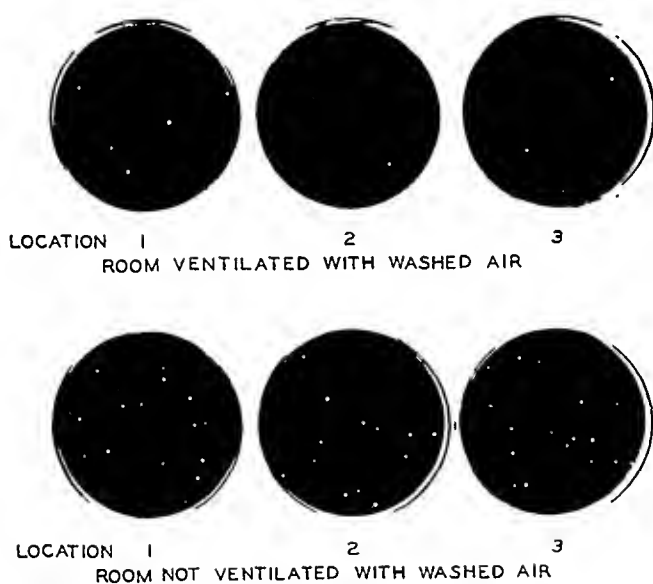


Fig. 7.—Twenty-four hour cultures of sterile Petri dishes of blood agar exposed in the same room under identical conditions and with every precaution taken to keep the room clean except that the lower plates were exposed first without use of the ventilating system while the upper plates were exposed with the ventilating system in use. In both exposures the room was unoccupied except for placing the plates. This “washing out” of the room with clean air did not completely eliminate the pathogenic bacteria. With a number of persons present, recontamination was rapid. With the use of every precaution an occasional infection occurred.

(243.8 cm.) from the lamp within sixty seconds. The carbon arc lamp was tried but had practically no effect on the organisms.

In the fall of 1934, various manufacturers of ultraviolet ray lamps were asked to cooperate in the experiments to the extent of furnishing the necessary equipment. A favorable contact was made with the Westinghouse Lamp Company, which has conducted extensive researches

in the generation and application of radiant energy, specializing in those regions of the spectrum which were found to be bactericidal. They advised us as to the wavelengths and intensities of radiation which were most efficacious for killing bacteria and least irritating to the tissues and supplied specially designed radiation tubes and other equipment for experimental purposes.

It is well recognized that the germicidal and fungicidal action of radiant energy depends on the wavelength of the radiation reaching

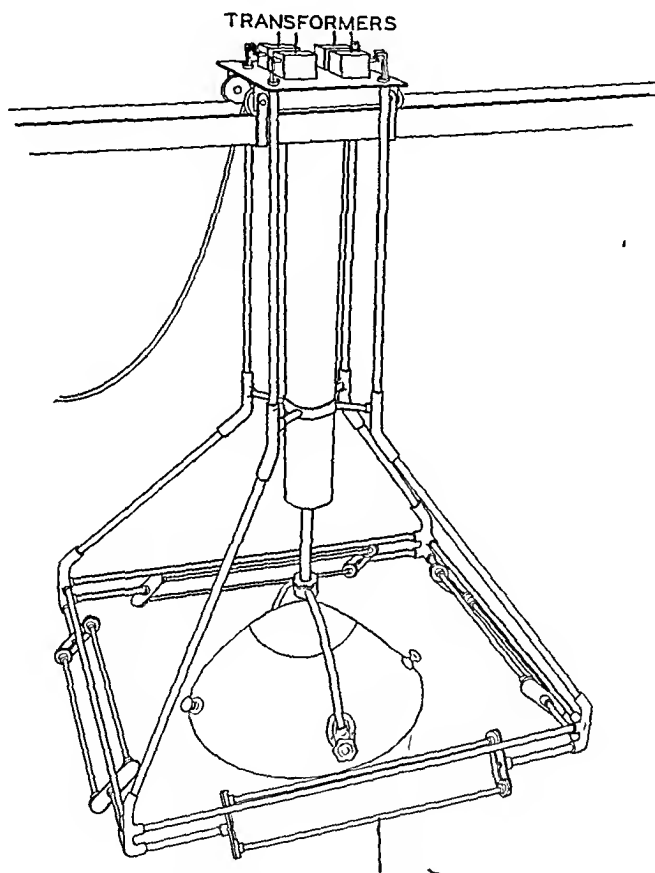


Fig. 8.—Arrangement of the special radiation tubes, each 30 inches long, about the operating room spot light as they were used in the following experiments. This illustration is made from an actual photograph taken from the student's observation room on the upper floor; the outline is inked in and the photograph bleached out. The opposite tubes are 5 feet apart and are so placed that their radiations are directed beneath the spot light. The operative incision and the supply and instrument tables were always exposed to some of the radiations. This arrangement was made with the idea of sterilizing the room if possible but with the definite plan of laying down a barrage of bactericidal radiation of such an intensity that any organisms floating in the air would be killed before they could settle on the supplies and instruments or in the wound.

the organisms. The destructive action of this radiation, such as the erythema effect when living tissue is exposed, is also dependent on the wavelength and the amount of exposure.

It is at once evident that when long exposures are necessary, as for lengthy operations, it is not only desirable but imperative that the nature of the radiation (wavelength distribution and intensity) used for bactericidal action must be so selected that under all conditions a harmful burning action is avoided.

In designing a source of radiant energy which would prove effective in destroying bacteria, care had to be exercised to see that the intensities of the wavelengths capable of producing detrimental effects, such as erythema, were so low that such effects were practically nil. However, it was also of importance to provide a sufficiently high level of bactericidal radiation to accomplish destruction of the bacteria without the intensity being of such a character as to create any discomfort to the patient. To meet these requirements a special radiant energy device was designed and constructed by the Westinghouse Lamp Company. This device is tubular, has unheated electrodes and utilizes a special mixture of gases in which the discharge takes place with the production of radiant energy of the character mentioned. During operation the tube remains at a temperature only a few degrees above room temperature.

An operating room was equipped with eight of these lamps, each 30 inches (76 cm.) long, as shown in figure 8. Two blond volunteers from among the students were exposed to the radiation from these tubes for eighty minutes and received only a slight reddening of the exposed area, which disappeared within twenty-four hours.

Blood agar plates sprayed with *Staph. aureus-haemolyticus* and also with a mixture of organisms were exposed to this radiation in the approximate position of the operative wound. The plates were 4 feet (122 cm.) below the center of the cluster of tubes (fig. 8) and 5 feet (152 cm.) from the middle of the individual tubes. With eight tubes operating we could kill a lightly sprayed culture of *Staph. aureus-haemolyticus* within sixty seconds (fig. 9) or a heavily sprayed culture within less than five minutes (fig. 10). Control experiments showed that radiation did not affect the culture mediums.¹⁷

It was then determined that in the outlying parts of the room 13 feet (396 cm.) from the center of the cluster of tubes the number of organisms in the air could be greatly reduced within one hour of exposure but not completely eliminated (fig. 11).

17. Many of the cultures were made by Dr. John Devine, who is working with me on the effect of the radiation from these devices on various organisms (to be published).

In the next experiments the tubes were operated for thirty minutes, and then the plates were exposed for one hour after the tubes were turned off. There was a definite reduction in the number of organisms, but the air rapidly became contaminated again.



Fig. 9.—Forty-eight hour culture of blood agar plates lightly sprayed with a filtered solution of *Staph. aureus-haemolyticus* and exposed to the eight tubes in the approximate position of an operative wound (5 feet from the individual tubes). There was a marked reduction in the number of colonies after thirty seconds' exposure and all organisms were killed within sixty seconds.

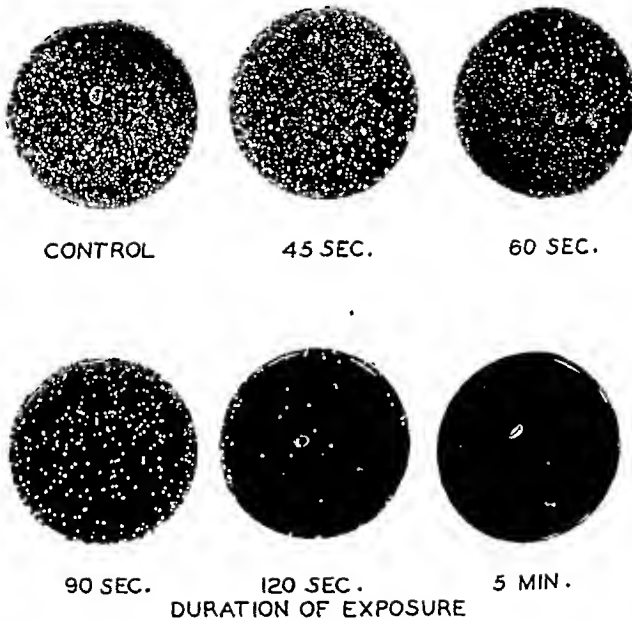


Fig. 10.—Experiment similar to that shown in figure 9, except that the plates were sprayed heavily with an unfiltered suspension of *Staph. aureus-haemolyticus*. Most of the organisms were killed within two minutes, and all but one colony within less than five minutes. About the periphery of the plates the organisms were shaded from some of the lamps by the edge of the Petri dish and received a less intense exposure and consequently survived for a longer period of time than those in the center. Likewise, where the organisms were in clumps some of them were partially protected and a longer period of exposure was necessary for complete sterilization.

Culture plates of blood agar sprayed with hemolytic staphylococci were then exposed at varying distances from the tubes for periods of time varying from ten minutes to one hour, showing that the time required to kill organisms varied with the distance from the tubes, as in figure 12. Practically all organisms exposed to the radiation from these tubes at a distance of 8 feet or less from the center of the cluster were killed within less than ten minutes and at a distance of 10 feet (304 cm.) within less than thirty minutes. Organisms shaded by the glass edge of the Petri dish were not killed within this time.

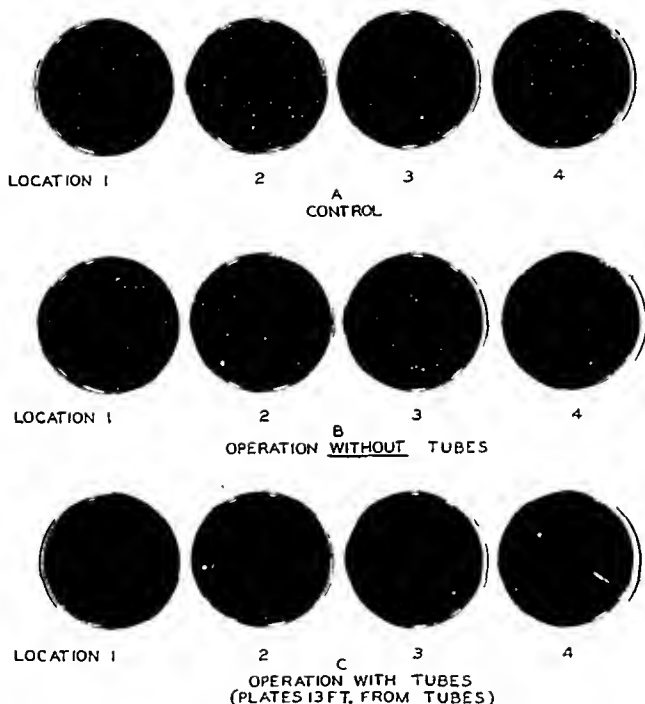


Fig. 11.—Plates exposed in the corners of the operating rooms 13 feet from the center of the cluster of tubes (11 feet from the nearest tube) for one hour and cultured for twenty-four hours. The three exposures were made during three consecutive hours, as follows: while the room was being set up for the operations without the use of the tubes (*A*); during the first operation performed without the tubes burning (*B*), and during the second operation performed with the tubes burning (*C*). Conditions were identical except for the additional personnel necessary for the operations. There was a great reduction in the contamination of the air even at a distance of 13 feet during the operation with the tubes burning, at which time, with more persons and longer occupancy, the contamination of the air should have been at the maximum.

Since there is always a continuous contamination of the air by the operating team and since the outlying parts of the room could not be completely sterilized with the eight tubes in use, it was thought neces-

sary to turn on the tubes during the operations. By this means we hoped to be able to lay down a barrage of radiation which would kill any organism before it could float into the field and drop into the wound. It was felt that if this could be accomplished without injury



Fig. 12.—Petri dishes of blood agar sprayed with a filtered suspension of *Staph. aureus-haemolyticus* and exposed in the locations shown. The organisms nearest the tubes were quickly killed; those exposed at 8 and 10 feet were killed within less than thirty minutes, while those protected by the shadow of the edge of the Petri dish were not killed within this time.

to the tissues we could eliminate the occasional gross infection. Furthermore, by eliminating contamination of the wound which must always occur but which only rarely goes on to suppuration, we could make

the postoperative course of all patients much smoother. We could also prevent as great a postoperative rise of temperature as occurs in patients operated on without this sterilization of the air. Wounds in rats were exposed for as long as thirty minutes and found to heal as well as, if not better than, those in the control animals for whom the radiation was not used. The peritoneum was exposed for the same length of time, and there was no apparent damage and no resultant adhesions. Wounds in dogs are now being exposed for ninety minutes, and healing is apparently quite satisfactory.¹⁸

A temporary protection for the staff was devised (fig. 13), and operations on patients were started. Repeated cultures from the air during two successive operations, the first without and the second with the tubes burning, showed that practically all organisms in the air within

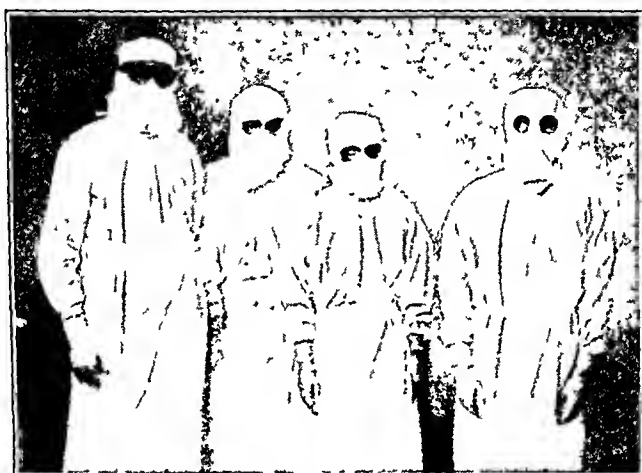


Fig. 13.—Photograph illustrating the manner in which the members of the staff were protected. The eyes were covered with goggles of plain glass, which is impermeable to the radiation. An eye shade was also used by some to cover the vents in the goggles. The remainder of the head was covered with a hood of starched cloth. The goggles limit the side vision and tend to become foggy, and it is quite hot beneath the hood. Steps are now under way to provide a more comfortable protection for the operating room personnel.

a radius of 8 feet of the operative incision could be killed (figs. 12 and 14). All exposed supplies and instruments were thus within the effective range of the radiation emanating from these tubes.

From the first trial our results were most gratifying. The patients had less postoperative pain, and healing was more rapid (figs. 15 and 16). All wounds made with the tubes burning maintained throughout the period of healing a dry, scaly appearance (figs. 15 and 16),

18. Experiments on animals have been carried out in conjunction with Dr. Paul Sanger, and these results will be published at a later date.

as contrasted to the occasional moist, slightly macerated appearance of the suture line in thoracoplasties heretofore performed. As contrasted to the high temperature in the occasional patient with an infection of the wound (fig. 17) and the moderate elevation seen in a group of patients with no gross evidence of infection (fig. 18 *A*), there was little rise of temperature in any patients operated on in the field of radiation from these tubes (fig. 18 *B*). Comparable temperature curves

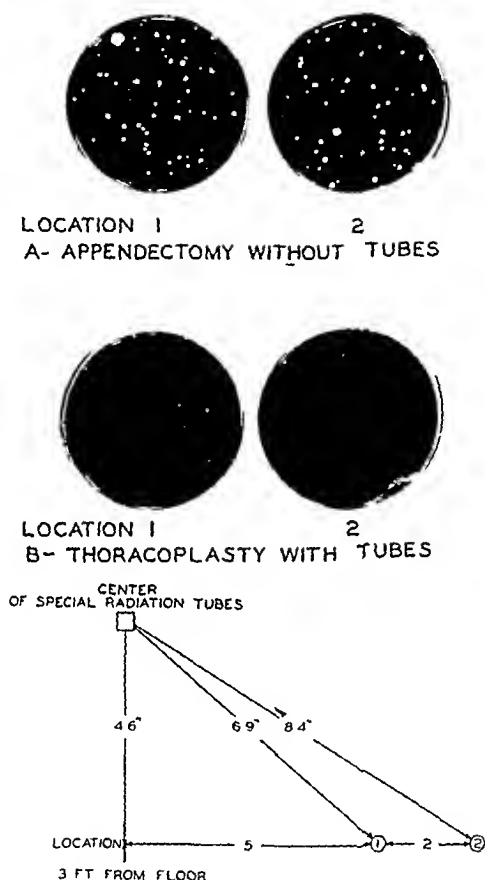


Fig. 14.—Forty-eight hour cultures of sterile blood agar plates exposed to the air for one hour in the locations shown. All conditions, including the operating room personnel, were identical except that the plates shown at *A* were exposed without the tubes burning for the first hour and those at *B* with the tubes burning for the second hour when the contamination of the air should have been greater. Only three colonies are seen in *B*, and one of these is near the rim, where after falling on the plate it was protected from the radiation.

for two days after thoracoplasty in three successive cases in which radiation was used and in three successive cases in which radiation was not used are shown in figure 19. These were taken from the temperature charts used to make the composite curves shown in figure 18 *B*.



Fig. 15.—Photograph of the scar of a thoracoplasty wound nine days after the first stage, at which time parts of four ribs and transverse processes were removed. The maximum elevation of temperature was 38.2 C. (100.7 F.), while the average for the first three days was 37.21 C. (98.9 F.).

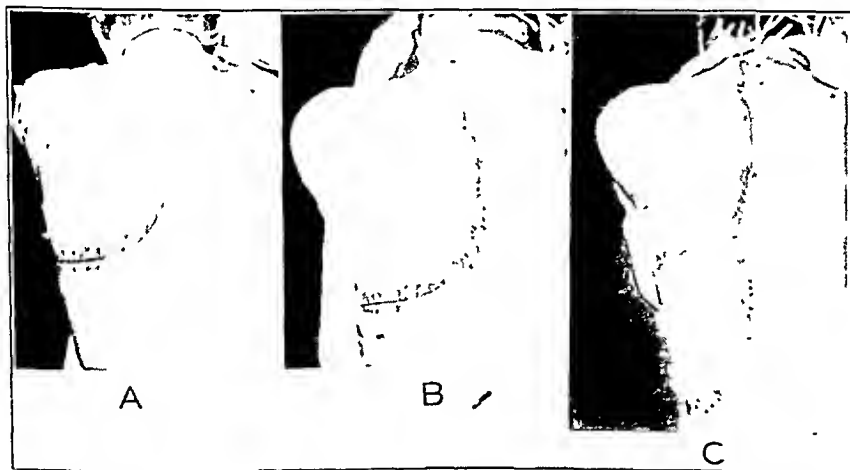


Fig. 16.—Extrapleural thoracoplasty showing the scars of three successive operations for the removal of parts of eleven ribs. This patient was considered to be a poor risk, and delay between stages was longer than usual. *A*, shows the scar eighteen days after removal of part of the three upper ribs. This picture was taken the day before the second stage. *B* shows the scar after the second operation was performed through the scar of the first and parts of four ribs were removed. This picture was taken nine days after operation and one day after the sutures were removed. *C* shows the scar of the third stage the day the sutures were removed and seven days after operation. The upper end of this incision extended into the old scar, so that for a short distance three operative incisions have been made through the same area. The third operation was performed fifteen days after the second. We are afraid to reopen, at such an early date, wounds not produced under this bactericidal radiation because of the danger of infection from organisms which may still be present and in larger numbers than at the time of the original contamination.

They well illustrate the great reduction in the postoperative rise in temperature in all (over fifty) patients so far operated on in the field of radiation from these tubes for various major surgical conditions. The patients were less ill, the convalescence was smoother and recovery was more rapid than had been the case heretofore.

Cultures were made of all drains, but in no case was there a growth. Incisions were reopened (thoracoplasty) within two to three weeks and were closed without drainage (fig. 16); no patient became infected, and there was little elevation of temperature (figs. 18 and 19). The undrained incisions in no case showed enough moisture along the incision or around the sutures to get a satisfactory culture, and no growth could be obtained. This was in sharp contrast to the thoracoplasty

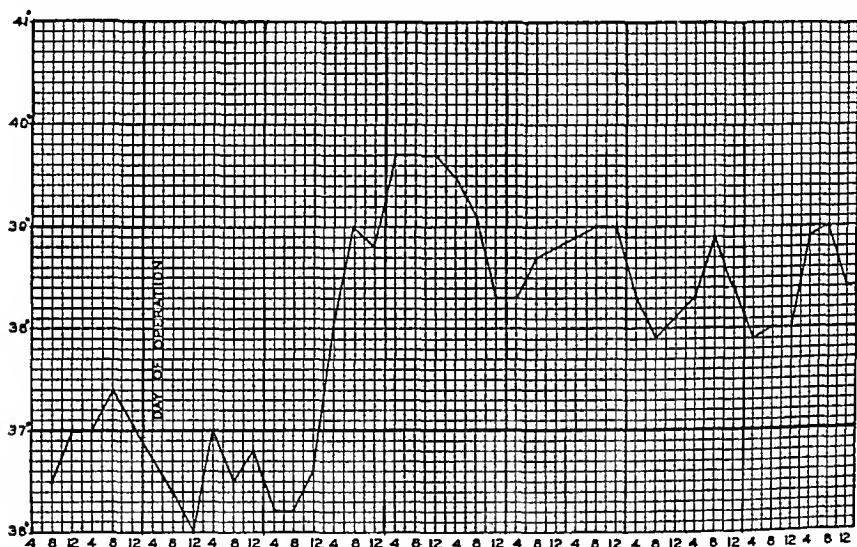


Fig. 17.—Temperature curve of a patient on whom the last thoracoplasty was performed before the introduction of the radiation tubes. The patient, operated on in October, died nine days after operation as a result of an overwhelming infection with *Staph. aureus-haemolyticus*. Because of the danger of infection, other patients in the hospital for an extrapleural thoracoplasty were discharged to wait until summer or until an operating room could be equipped with special radiation tubes and tests made to determine their safety and efficiency in killing the bacteria in the air.

wounds in earlier cases in which a positive growth of *Staph. aureus* was obtained from 33 per cent of the operative wounds, most of which were not grossly or clinically infected.

SUMMARY

In attempting to avoid the occasional operating room infection the following facts were established so far as our operating rooms and personnel were concerned:

1. Most of the infections were caused by *Staph. aureus-haemolyticus*. The organisms entered the wound from the air rather than from the skin of the patient. The air was contaminated by the operating room personnel and patients.

2. While gross infections with suppuration were rare, cultures of drainage tracts and incisions in many cases showed the presence of *Staph. aureus-haemolyticus* (as high as 33 per cent in cases in which thoracoplasty was performed).

3. All supplies and all procedures in operating room technic were checked by cultures and found to be satisfactory except for the air.

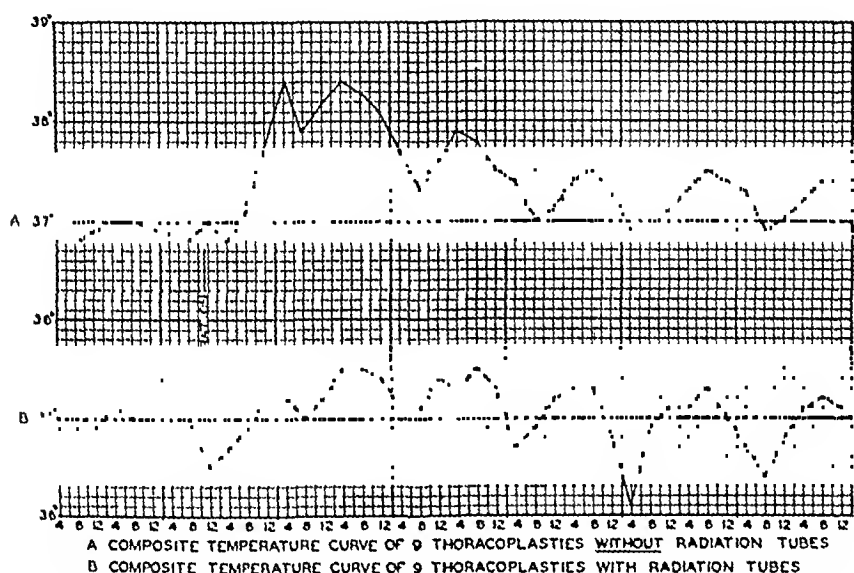


Fig. 18.—*A* is a composite curve of the temperatures of the last nine patients on whom thoracoplasty was performed during the summer before operation in the fatal case referred to in the legend for figure 17. None of these patients had a gross infection of the wound, and the postoperative clinical course was considered to be normal. Cultures of the wounds, however, showed a growth of *Staph. aureus-haemolyticus* in 30 per cent of the operations. *B* is a composite curve of the temperatures of the first nine patients on whom thoracoplasty was performed after operation in the fatal case referred to in the legend for figure 17 and with the use of the special radiation tubes. These operations were performed in January and February, during the worst epidemic of influenza and infection of the respiratory tract encountered during the past several years. The temperature curves *A* and *B* might well represent the difference in the entire convalescence of these two groups of patients.

which was heavily contaminated. *Staph. aureus-haemolyticus* was usually present, at times in large numbers.

4. The operating room personnel and the general population were found at times to have *Staph. aureus* (frequently hemolytic) in the

cultured from the wound was identical with the one cultured from the air during the operation.

8. Tubes specially designed to produce controlled intensities of the most effective bactericidal radiation are now used to sterilize the air with the following results:

(a) Sprayed cultures (*Staph. aureus-haemolyticus* and a mixture of many organisms) were killed at a distance of 5 feet within less than one to five minutes, the time depending on the density of the inoculation.

(b) With the tubes burning, practically no organisms could be cultured from the air within a radius of 8 feet from the operative field.

(c) In the corners of the room (13 feet from the center of the cluster and 11 feet from the nearest tube) the number of viable organisms falling out of the air was reduced by from 60 to 90 per cent.

(d) The air of the entire room could not be completely sterilized within one hour with only eight tubes, as shown in figure 7, and when they were turned off, recontamination quickly occurred if people were present.

(e) Blond persons exposed to the eight tubes for eighty minutes at a distance of 5 feet received only slight reddening of the exposed area, which cleared within twenty-four hours.

(f) Wounds in rats exposed to the eight tubes at a distance of 5 feet for thirty minutes healed better than in the control animals. No adhesions followed a similar exposure of the peritoneum.

(g) All patients operated on under the radiation from these tubes have had an unusually smooth convalescence. There have been no infected wounds, and no culture of material from the wound has shown a growth (approximately fifty patients have been operated on, two for an ulcerated carcinoma of the breast). There have been less elevation of temperature, less pain and a smoother and more rapid convalescence than in the control group of patients.

CONCLUSIONS

It is our opinion that as surgery has embraced operative procedures of greater magnitude and with inevitable trauma, the air-borne organisms have become a distinct hazard. The concentration of operative work by the increased utilization of operating room space has added to the danger of infection from air-borne organisms (in our experience predominantly staphylococci but occasionally streptococci).

It is our opinion, based on experience with this work, that many of the operative wound infections with staphylococci, which heretofore have been ascribed to contamination of the skin, are air borne. These have been combated by meticulously covering the skin, discarding the

knife used for the incision in the skin, changing the methods of preparing the skin, etc., but with little results in reducing the infections. They have recently been eliminated by us in a small series of cases (over fifty) by sterilizing the air with tubes emanating special bactericidal radiation. We do not advocate discarding the precautions used in skin technic, but each surgeon should give critical consideration as to whether the skin or the air is the source of organisms causing these infections. Tubes specially designed to produce controlled intensities of the most effective bactericidal radiation and arranged as shown in figure 8 will kill practically all the organisms in the air within a radius of 8 feet of the operative wound, and it is our opinion that when they are used the so-called skin-contaminated wounds will practically disappear.

The room can be practically sterilized by the use of additional tubes, but at present this does not seem to be necessary. Sterilization of the air should close the last great possible source of contamination of operative wounds. With our small series of patients (approximately fifty) there has been no case in which organisms could be demonstrated in the wound by washings and culture at the operation or at any time during the postoperative course. It is our opinion that it will soon be possible to eliminate almost completely operative wound infections in clean operations.

It should be emphasized that this is a preliminary report on the use of special radiation tubes for the control of air-borne organisms in the operating rooms. Many phases of this work are still under investigation, and it will require a longer time and a much larger series of cases to determine its full value. For us, it has already restored confidence in our ability to establish surroundings in which we can operate without danger of infection from organisms dropping in the wound. We now operate without fear of infection, whereas formerly the dread of bacterial contamination from an uncontrollable source was ever present.

REPAIR OF FACIAL DEFECTS

WITH SPECIAL REFERENCE TO THE SOURCE OF SKIN GRAFTS

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NEW YORK

The repair of a defect on an exposed part of the body, such as the face or neck, presents certain special problems. No matter where a raw surface occurs, it should be covered promptly in order to expedite healing, restore comfort and reestablish proper function. If it is on an exposed area, the added factor of appearance must be considered.

It is not the purpose of this communication to describe the technic involved in obtaining and applying different types of grafts and flaps but to consider their respective suitability for the repair of various defects of the face and neck. The possibilities of deformity in these regions are so vast and varied, owing to a wide range of congenital, traumatic and surgical causes, that to a certain extent each case must be considered an individual problem. Several accepted procedures may suggest themselves for the repair of a given defect, and it is not always easy to decide on the method which best suits the requirements of the particular case.

GENERAL CONSIDERATIONS

So far as it is possible to generalize, the attainable cosmetic result is a decisive factor in the selection of a procedure—subject, of course, to the size, location and etiology of the deformity, the vitality of the surrounding structures, the age and sex of the patient and the simplicity of the methods under consideration. In an old man the cosmetic element would not loom as large as in a young woman, while in the latter appearance is so important as to outweigh even simplicity of technic. The tissues employed in the repair must resemble the surrounding structures as nearly as possible, even if slight additional scarring is entailed, and they must be such as to retain their characteristics in the distant future. The sliding or rotating flap is the ideal procedure in every case, but skin may not be available for this because of the size or location of the defect (figs. 1 to 6).

When a defect cannot be eradicated by approximating the surrounding edges of the skin, the choice lies among various types of free grafts

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and tubed pedicle flaps. Here the determining factors are the accessibility of material, harmony of the transposed skin with its new surroundings and absence of secondary deformity. A graft is not a success merely because it "takes" perfectly; it must match the skin around it in color and texture.

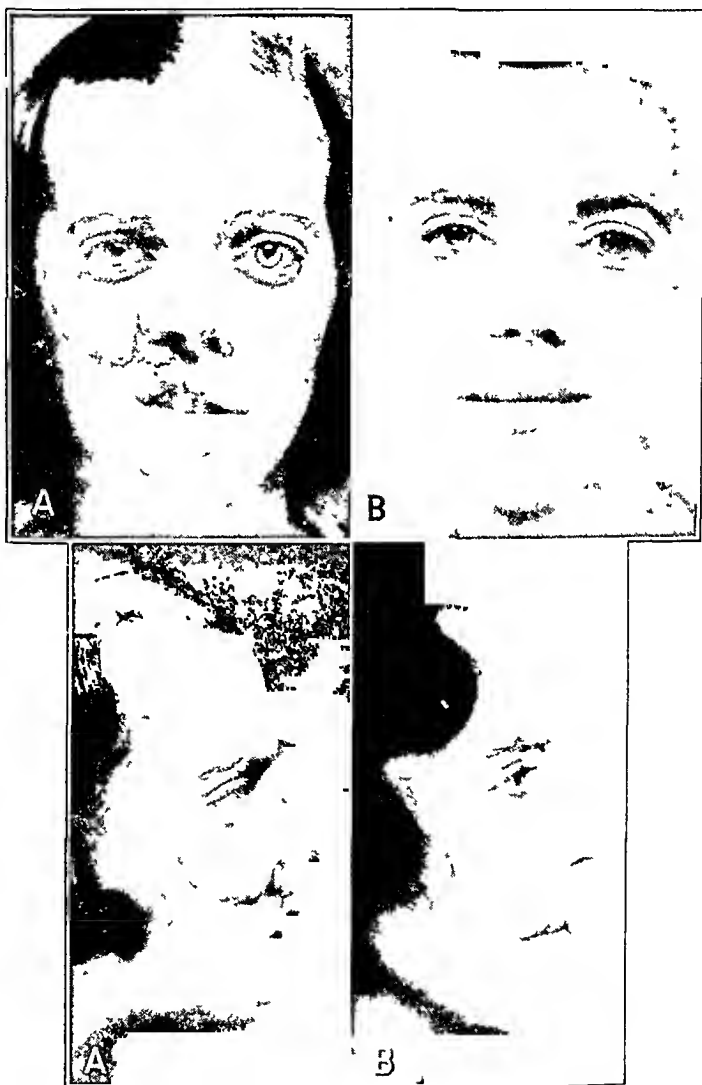


Fig. 1—*A* shows partial loss of the upper lip, distortion of the lip and nostril, a depressed scar of the cheek and nasal fracture following an injury in an automobile accident. The lumpy area directly under right nostril (fig. 2 *N*) is from the displaced skin of the lip which was improperly sutured in the emergency repair. After excision of all scar tissue the curled skin area was flattened out and sutured into surrounding skin, as shown in *B*. The position of the nostril was corrected, and the nasal fracture was reduced. An ascending pedicle flap from the cheek (fig. 2 *F*) was sutured into the lip to bring about its normal position.

Since it is extremely difficult to harmonize skin from remote parts of the body with that of the face, a pedicle flap from the forehead, cheek or neck is to be preferred. I advocate these sources in spite of the scarring entailed, as a glaring patch of alien skin is far more conspicuous, in my opinion, than a hair-line scar. Whenever possible, the dimensions of the flap from the forehead are reduced to a minimum by serial excision of the deformity. If the flap is kept small enough, the

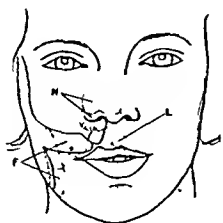


Fig. 2.—A drawing illustrating the repair done in figure 1. *F* indicates the ascending flap from the cheek for filling out the defect of the lip; the distorted portions of the lip and nostril were replaced in the position shown by continuous lines (*N*).

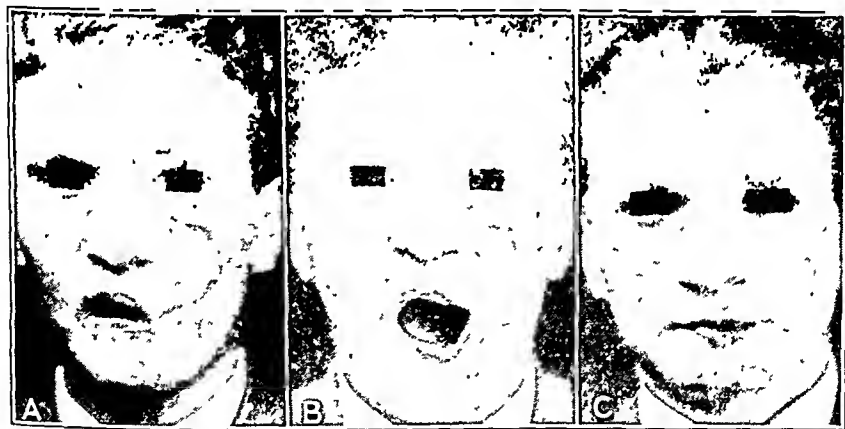


Fig. 3.—*A* shows partial loss of the lower lip with distortion of the mouth following an injury in an automobile accident. The function of the mouth was limited by cicatricial adhesions. The missing mucous membrane and vermilion border of the left side of the lower lip were reconstructed by a mucous membrane flap from the upper portion of the cheek, as shown in *B*. The scarred central portion of the lip involving the mucous membrane and the skin was repaired by shifting of three flaps (fig. 4, *A*, *B* and *C*). *C* shows the final result.

resultant defect can be closed without secondary grafting, owing to the elasticity of the skin of the scalp and forehead (figs. 7 and 8).

From the point of view of color, if for some reason a flap of skin from the forehead is not available, the second choice for use on the

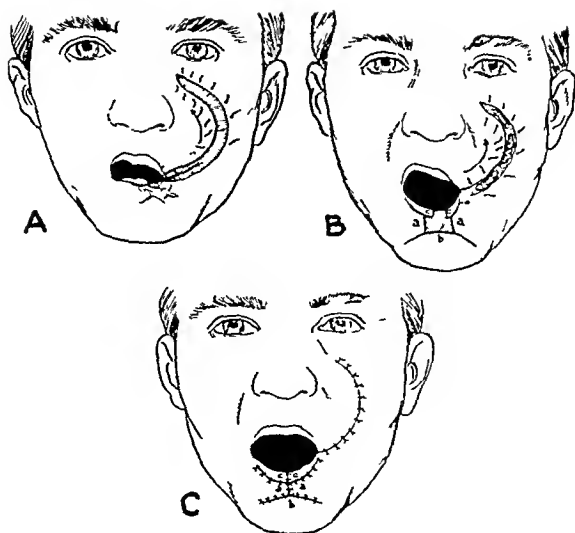


Fig. 4—A drawing illustrating the technic of repair used to attain the end-result shown in figure 3 C. *A* shows excision of the scar of the cheek and the formation of a rectangular mucous membrane flap on the upper cheek (circumscribed in the dotted lines) to reconstruct the left half of the lower lip. *B* shows excision of the central scar of the lower lip and repair of the defect by flaps *a*, *b*, and *C*, the final result.

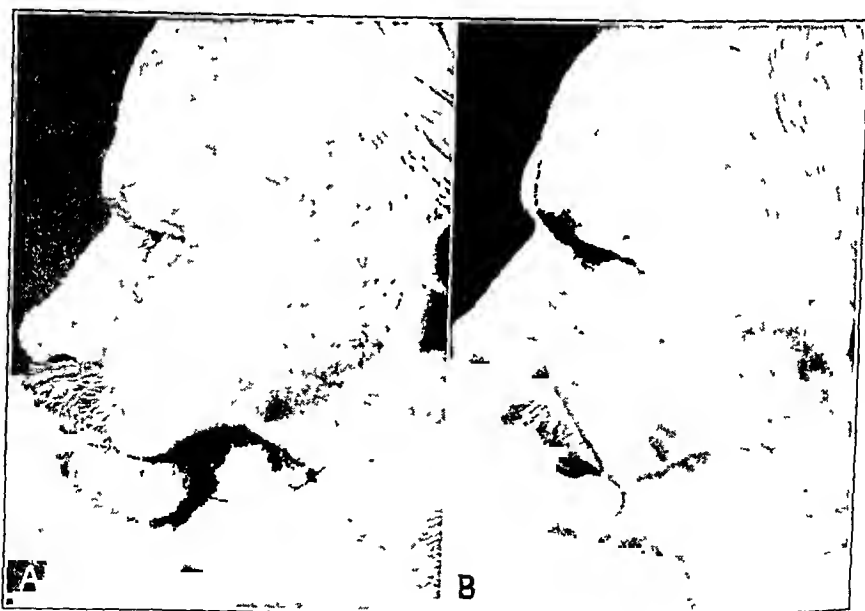


Fig. 5.—*A* shows a defect of the cheek in a man of 64 following partial removal of the lower jaw for osteomyelitis. Repair was done by utilizing the surrounding skin for lining and rotating the skin from the cheek and neck to provide the covering with the end-result shown in *B*. By extensive undermining and rotating the facial skin, it is possible to repair large defects which might otherwise require skin from distant parts. The cosmetic end-result is always superior when the methods described here are used.

face is skin from the back of the ear. In most cases the retro-auricular skin is preferable to that of the middle and lower portions of the neck, as the latter presents a marked contrast, even after a period of years, according to my experience. In men, skin from the hair-bearing upper portions of the neck is useful for the reconstruction of hairy facial areas (fig. 8).

Accessibility is a strong argument in favor of the neck as a source of skin for facial reconstruction. A flap from this region can usually be tubed, and the secondary defect is easily closed, with the suture line concealed in the natural folds of the neck. This type of flap is particularly valuable for the replacement of losses in the lower half of the facial skeleton.

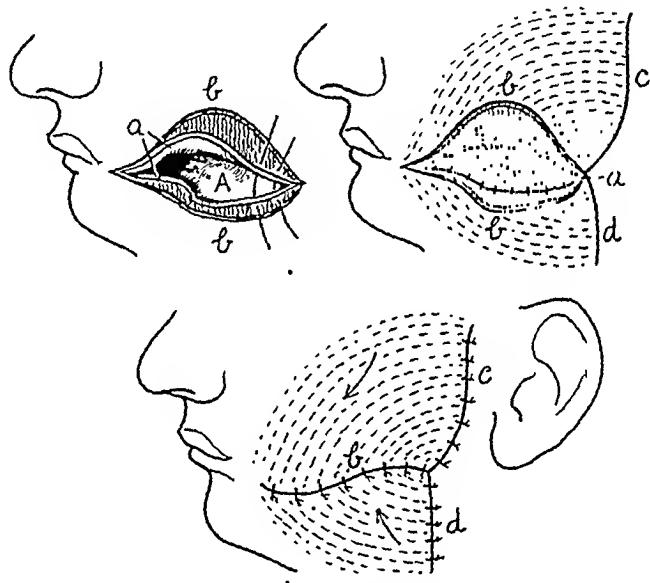


Fig. 6.—Drawing of operative procedure used to attain the end-result shown in figure 5 B. The skin turned for the lining is indicated by *a*; the undermined skin of the cheek and neck, by *b*, and the relaxation incisions by *c* and *d*. *A* indicates the tongue.

The ascending flap from the cheek provides a skin supply of excellent quality (figs. 1 and 2), as does the descending flap from the nasolabial fold and the lateral nasal wall; however, the latter type is more subject to limitations of size because of the proximity of the nostril and the inner canthus.

When a large amount of skin has been lost on the face or the tissues surrounding the defect have been devitalized (as by x-rays, radium or malignant disease), skin must be sought on a distant part of the body, but the end-result is hardly ever entirely satisfactory from the cosmetic point of view. The brachial flap, for example, has a good blood

supply, and the transposed skin is very thin, but the color does not match that of the face.

Other common sources of skin flaps for the repair of large facial defects are the abdomen, back and chest (fig. 11).



Fig. 7.—*A* shows two views of a woman aged 35 who had paraffin injected into her nose twenty years previously for a saddle-back deformity. Ten years later the nose began to shrink, and the nasal skin was invaded by a paraffinoma. After excision of the involved nasal skin and subcutaneous structures the defect was repaired by a flap from the forehead and insertion of a cartilaginous support from the rib, with the end-result shown in *B*.

In women with hypertrophied pendulous breasts, the posterior mammary surface is another excellent source of skin supply. The skin from

this area is satisfactory for the reconstruction of a large defect, although it is lighter in color than the facial skin; the deformity of the breast can be repaired at the same time.

Comparing the merits of various types of free skin grafts, I favor in general the thin graft (epidermal and dermo-epidermal) for the covering of a large body surface and the full thickness graft on the face, forehead, eyelids and cheeks and on areas requiring pressure, such as the palms of the hands and the elbow. Thus grafts from the upper lids and fine retro-auricular skin are useful for covering defects of the eyelids, wherein the clumsier pedicle flap is too heavy and the



Fig. 8.—*A* shows the loss of the right lower half of the nose, slightly involving the cheek and lip, with a radium ulcer of the floor of the nose and septum. The condition was produced by prolonged radium therapy for epithelioma of the right nostril. Healing of the ulcer was brought about by deep pinch grafting. Reconstruction was started about six months after complete healing of the wound. A small triangular flap was turned up from the nasolabial fold toward the apex of the defect to cover the missing part of the cheek and lip, as shown in *B* and *C*, *c*. *C* illustrates the repair diagrammatically. The skin flap (*B*) is sutured to the freshened edges of the defect, serving as a lining. A flap from the forehead (*A*) was used for covering and a small flap (*C*) from the nasolabial fold to cover the defect in the cheek. The final result after excision of the scar on the forehead is shown in *D*. No skin graft is required to cover this type of defect. Three years after operation was completed there was a recurrence of the malignant growth in the central portion of the upper lip, which required extensive excision of the lip and the central portion of the maxilla.

Thiersch graft is debarred by considerations of color. On the whole, however, the popularity of the split (dermo-epidermal) graft is fully justified by its end-results. Its preparation is more simple than that of the full thickness graft, its "take" is more certain and the cosmetic effect is frequently little inferior to that of the Wolfe graft. I prefer it in numerous circumstances, viz., to cover burned areas on the extremities, to epidermize extensive surfaces of the body, thereby reducing the period of convalescence and avoiding secondary infection and contracture, and to replace mucous membrane in facial cavities.

Often when a defect is replaced, the reconstructed area must be raised because of nondevelopment or destruction of subcutaneous tis-



Fig. 9.—*A* shows the loss of the nostril near the nasal tip, with scarring of the skin and a scar defect of the chin following an injury in an automobile accident in childhood. The patient had an oversized type of nose prior to the accident. The end-result following repair, shown diagrammatically in figure 10, is pictured in *B*.

sues. Full thickness skin, deprived of epidermis, has been used successfully for this purpose.

PARTICULARIZED APPLICATION

The location of the defect is an important factor in the selection of the reparative procedure. For a nasal defect, for example, the skin from the forehead, as I remarked earlier, is so superior to any other in texture and color that it should be used in spite of the added scar. Only if skin from the forehead is not available is a flap from the neck,

chest or arm used. A graft from the eyelid or a retro-auricular graft is indicated for filling out a defect on the nose and upper lip, where shifting of skin is difficult; the color, however, is not as good as that of a flap from the forehead.

Some nasal defects can be repaired by rotating the entire thickness of the nasal wall—skin, cartilage and mucous membrane. This procedure, when done in stages, often obviates the necessity for grafting (figs. 9 and 10).

It is possible to correct a small depression of the middle portion of the nose, especially after submucous resection, by transposing the lateral cartilages, which are fixed at the dorsum.¹ This method of utilizing the surrounding nasal structures has proved satisfactory in my experience.

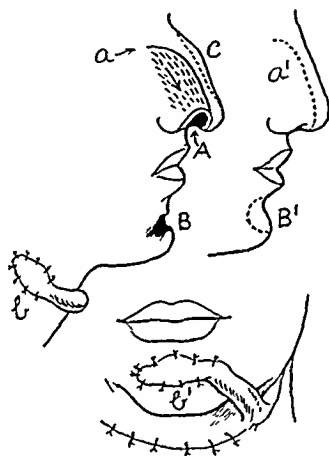


Fig. 10.—Drawing illustrating the procedures of repair used to attain the end-results in figure 9 *B*. To make possible the correction of the defect in the nostril by shifting the lateral wall, the nose was shortened and the oversized part of the dorsum was removed. The defect (*A*) was covered by rotating the surrounding structures (*a*) and suturing along the line *a'*. The defect in the chin (*B*) was repaired by a tubed flap from the neck *b'*.

Autogenous cartilage is always the substance of choice for repair of the nose and resistant parts of the facial skeleton, such as the forehead, chin and zygoma. In the past few years I have used dermal grafts for filling out facial depressions, and although I have obtained excellent results in all instances, sufficient time has not elapsed to pass final judgment on this medium.

1. Maliniak, Jacques W.: Correction of Nasal Depressions by Transposition of the Lateral Cartilages: A New Method, *Arch. Otolaryng.* **15**:280-284 (Feb.) 1932.

in spite of the added scar. For a defect on the cheek, the combined use of serial excision and a flap from the forehead minimizes secondary scarring and secondary grafting on the forehead. The flap from the forehead is particularly recommended for the restoration of nasal losses.

A tubed pedicle flap from the neck is valuable for reconstruction of the lower half of the facial covering. A large surface on the neck is best covered by a delayed tube pedicle or migrating flap from the lateral aspect of the chest and abdomen.

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EFFECT OF PARTIAL GASTRECTOMY ON GASTRIC ACIDITY

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AND

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OMAHA

Partial gastrectomy has in recent years been coming more and more into prominence in the treatment of duodenal ulcer. The all too frequent occurrence of marginal ulcer after gastro-enterostomy has led surgeons to seek some method of approach to the problem of duodenal ulcer by which the acidity of the gastric secretions could be reduced and the incidence of marginal ulcer diminished. The studies of Klein,¹ Lewisohn and Ginzburg,² Lewisohn and Feldman,³ de Takáts,⁴ Winkelstein,⁵ Crohn,⁶ Wilensky and Crohn,⁷ McCann⁸ and others seem to leave little doubt that after partial gastrectomy there is a definite reduction in gastric acidity.

When one attempts to explain this reduction in acidity, however, one is confronted with a great deal of conflicting evidence; before the value of partial gastrectomy in the treatment of duodenal ulcer can be determined, some more definite information as to its mode of action is desirable. Several years ago Deaver⁹ was apparently under the impression that partial gastrectomy removed some of the acid-secreting area of the stomach and that this was the cause of the reduction, but it is now generally admitted that such an explanation is not satisfactory. Friedman¹⁰ and Crohn⁶ stated that there is some nerve center located

From the Departments of Experimental Surgery and Physiology, Creighton University School of Medicine.

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2. Lewisohn, R., and Ginzburg, L.: *Surg., Gynec. & Obst.* **44**:344, 1927.
3. Lewisohn, R., and Feldman, R.: *Ann. Surg.* **82**:925, 1925.
4. de Takáts, G.: *Am. J. M. Sc.* **172**:45, 1926.
5. Winkelstein, A.: *Am. J. Surg.* **7**:494, 1929.
6. Crohn, B. B.: *S. Clin. North America* **5**:53, 1925.
7. Wilensky, A. O., and Crohn, B. B.: *Am. J. M. Sc.* **153**:808, 1917.
8. McCann, J. C.: *Am. J. Physiol.* **89**:483, 1929.
9. Deaver, J. B., and Reiman, S. P.: Subtotal Gastrectomy, *J. A. M. A.* **85**: 1619 (Nov. 21) 1925.
10. Friedman: *Zentralbl. f. Chir.* **49**:1621, 1922.

near the incisura; that in doing a partial gastrectomy this nerve center is removed and that unless it is removed there will be little reduction in acidity. There has been, however, little evidence shown to substantiate this theory. Babkin,¹¹ Klein,¹² Ivy and Whitlow¹³ and Edkins¹⁴ expressed the belief, and have produced considerable evidence to substantiate their theory, that some reflex or humoral mechanism is responsible. Portis and Portis¹⁵ and Steinberg, Brougher and Vidgoff,¹⁶ on the other hand, stated that the most important factor in reducing acidity after partial gastrectomy is regurgitation of alkaline intestinal secretions into the stomach through the wide stoma produced by Polya's operation. That intestinal regurgitation is a definite entity and the mechanism by which reduced acidity is brought about, we¹⁷ have explained in a previous publication. Walters,¹⁸ in an editorial in a recent issue of *Surgery, Gynecology and Obstetrics*, stated that after partial gastrectomy acidity is reduced "because of dilution and neutralization of the gastric secretions by reflux of intestinal secretions rather than because of actual failure of the remainder of the stomach to secrete hydrochloric acid. Stimulating gastric secretion by injection of histamine in many cases will produce a measurable secretion of hydrochloric acid even after operation has been performed."

Histamine is a stimulus which probably acts directly on the acid-secreting cells of the stomach. It will act on isolated gastric pouches and is in a sense an artificial stimulus. The fact that the acid-secreting cells of the stomach continue to respond to it after partial gastrectomy probably has no important clinical significance as far as proposed operations for duodenal ulcer are concerned. Our investigations were done in an attempt to determine whether there is an actual failure of the stomach to secrete hydrochloric acid after partial gastrectomy, and if not, to evaluate the relative importance of dilution and neutralization in reducing the acidity of the gastric contents.

11. Babkin, B. P.: *Am. J. Digest. Dis. & Nutrition* **1**:715, 1934.

12. Klein, E.: *Gastric Section: V. Achlorhydria Following Partial Gastrectomy for Ulcer; Studies with Histamine and the Transplanted Gastric Pouch*, *Arch. Surg.* **30**:162 (Jan.) 1935.

13. Ivy, A. C., and Whitlow, J. E.: *Am. J. Physiol.* **60**:578, 1922.

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16. Steinberg, M. E.; Brougher, J. C., and Vidgoff, I. J.: *Changes in the Chemistry of the Contents of the Stomach Following Gastric Operations*, *Arch. Surg.* **15**:749 (Nov.) 1927.

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18. Walters, W.: *Surg., Gynec. & Obst.* **61**:267, 1935.

We¹⁹ have previously shown that after gastroduodenostomy has been performed there is a considerably greater amount of regurgitation of intestinal fluids into the stomach than there is after the two more commonly used operations, gastrojejunostomy and pyloroplasty. The acidity of the gastric contents nevertheless remains high after gastroduodenostomy, in spite of profuse reflux of duodenal fluid. Our first experiments, therefore, enabled us to make a comparison of the effects of gastroduodenostomy and partial gastrectomy with Polya's anastomosis and to determine whether there is sufficiently greater regurgitation after the latter operation to explain the low gastric acidity which it is known to produce.

METHOD AND RESULTS

The test meal used throughout in the present study was a specially prepared²⁰ 2 per cent concentration of Liebig's meat extract, slightly acidified with hydrochloric acid and containing a small amount of phenolsulfonphthalein. A meal containing meat extract was chosen because it has excellent secretogogic properties and furnishes a normal gastric stimulation. It also remains fluid in the stomach and lent itself admirably to the special chemical studies which we wished to make. Phenolsulfonphthalein was added because when alkalized it gives the meal a purple color which can be used as an index of the amount of dilution which the meal has undergone in the stomach. Samples of the meal removed from the stomach were compared with a sample of the original meal, and the percentage of dilution, as shown by a lessened concentration of dye, was read directly on a colorimeter.

Experiments were performed on healthy dogs which had been made to fast for twenty-four hours, and the procedure used was the same in all. The amount of the meal given varied between 600 and 900 cc., depending on the size of the dog and the emptying time of the stomach. The amount of the meal was adjusted so that fractional samples could be removed every half-hour for at least one and one-half hours.

A portion of each of the half-hour samples was alkalized, interfering substances were precipitated with sodium tungstate and sulfuric acid and the concentration of phenol red in each sample was compared on a colorimeter with that of a portion of the original meal similarly treated. The percentage of reduction in the concentration of phenol red in the samples removed from the stomach indicates the number of cubic centimeters of fluid which entered into and diluted each 100 cc. of the original meal during its stay in the stomach. This diluting fluid may be acid secreted by the stomach, a nonacid fluid secreted by the stomach or fluid which has entered the stomach from the small intestine.

We²¹ have previously shown that the nonacid fluid secreted by the stomach is small in amount, and for practical purposes it has been ignored in the present investigation. In order to determine the relative amount of dilution produced in the meal by acid secreted by the stomach and by fluid regurgitated from the intestine the

19. Hill, F. C.; Henrich, L. C., and Wilhelmj, C.: Changes Produced by Various Operations on the Stomach Shown by the Use of the Modified Acid Test Meal, *Arch. Surg.* **31**:622 (Oct.) 1935.

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following chemical analyses were made by a method previously described:²² (1) analysis of the acid chloride content of the original meal and (2) analysis of the acid chloride content of each of the samples removed from the stomach. The acid chloride content of each of the samples is compared with the acid chloride content of the original meal corrected for a dilution similar to that of the sample. This correction is made by multiplying the acid chloride content of the meal by the percentage of phenol red in the sample. If the acid chloride content of a sample is greater than the acid chloride content of the meal corrected for dilution, the difference represents the acid secreted by the stomach. If it is less, the difference represents neutralization. We²² have shown that the concentration of chloride in the secretion of the fundic portion of the stomach is practically all due to acid chloride and averages 578 mg. per hundred cubic centimeters. Thus, by dividing the extra acid chloride of a sample (the acid chloride in excess of what the original meal would have at that dilution) by 5.78, the quotient will represent the number of cubic centimeters of acid fluid which was secreted into each 100 cc. of the test meal.

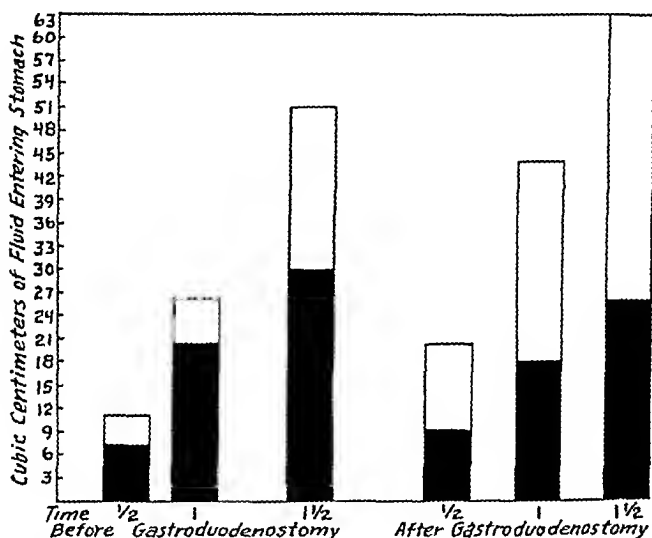


Fig. 1.—Chart showing the cubic centimeters of fluid per hundred cubic centimeters of the test meal entering the stomach of dog A before and after gastroduodenostomy. The columns of total fluid are divided into acid fluid (black) and nonacid fluid (white) and show the findings on fractional samples at half hour intervals.

The reading for phenol red subtracted from 100 gives the total amount of fluid which diluted each 100 cc. of the test meal. The difference between this total fluid and the acid fluid gives the amount of nonacid fluid which diluted each 100 cc. of the test meal.

In figures 1, 2, 3 and 4 we have shown graphically the average results of a large series of experiments done on four dogs before and after operation. Two of the dogs were subjected to gastroduodenostomy, and two, to partial gastrectomy with Polya's anastomosis. When partial gastrectomy was performed, the stomach

22. Wilhelmj, C. M.; Hill, F. C., and Neigus, I.: *Am. J. Physiol.* **106**: 381, 1933.

was resected at about the level of the incisura angularis, and the portion removed was carefully inspected to be sure that all of the pyloric region, and as little as possible of the fundic portion, were taken. These charts show the total amount of fluid which had entered each 100 cc. of the test meal at the end of each half hour period, and the total fluid is further resolved into acid and nonacid fluid.

In comparing the results of the two types of operation it will be noted that although the total amount of fluid entering the stomach is about the same in both

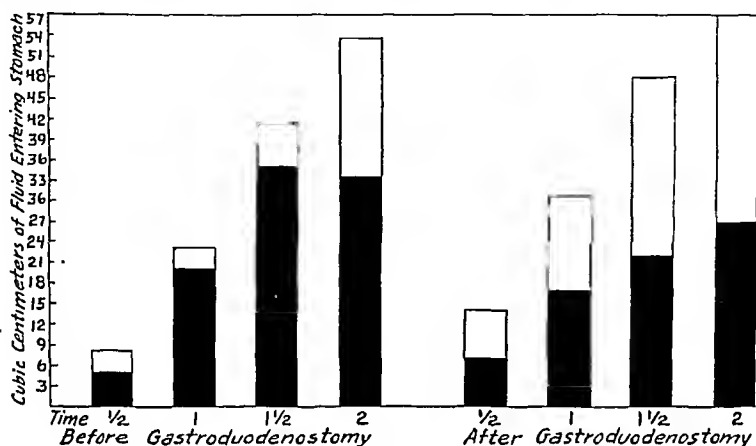


Fig. 2.—Chart showing the cubic centimeters of fluid per hundred cubic centimeters of test meal entering the stomach of dog B before and after gastroduodenostomy. The findings are indicated as in figure 1.

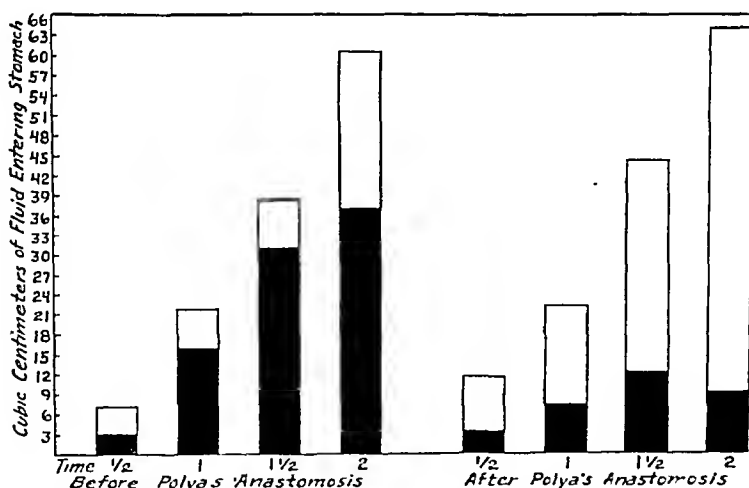


Fig. 3.—Chart showing the cubic centimeters of fluid per hundred cubic centimeters of test meal entering the stomach of dog C before and after partial gastrectomy with Poly's anastomosis. The findings are indicated as in figure 1.

instances, there is a great difference in the amount of acid fluid. In the dogs with resection there is a great reduction of acid, and since there is no correspondingly greater dilution of the meal, the only conclusion possible is that less acid is secreted by the stomach

In order to obviate the factors of neutralization of secreted acid and dilution of the test meal by regurgitation of intestinal fluids and to demonstrate directly the effect of partial gastrectomy on gastric acidity, another approach was made to the problem by utilizing whole stomach pouches. These pouches, illustrated in figure 5, were of four types. In one type the stomach was separated from the duodenum at the pyloric sphincter, and the ends of the stomach and duodenum were closed. The stomach was then severed close to the esophagus, and the end of the upper stump of the stomach was anastomosed to the side of the jejunum. The opening in the stomach was closed, and a portion of the wall of the closed pouch thus formed was pulled through a stab wound in the abdominal wall to form a gastrostomy opening. Studies were made on this type of pouch for comparison with studies on pouches prepared in a similar manner except that the pyloric end of the stomach

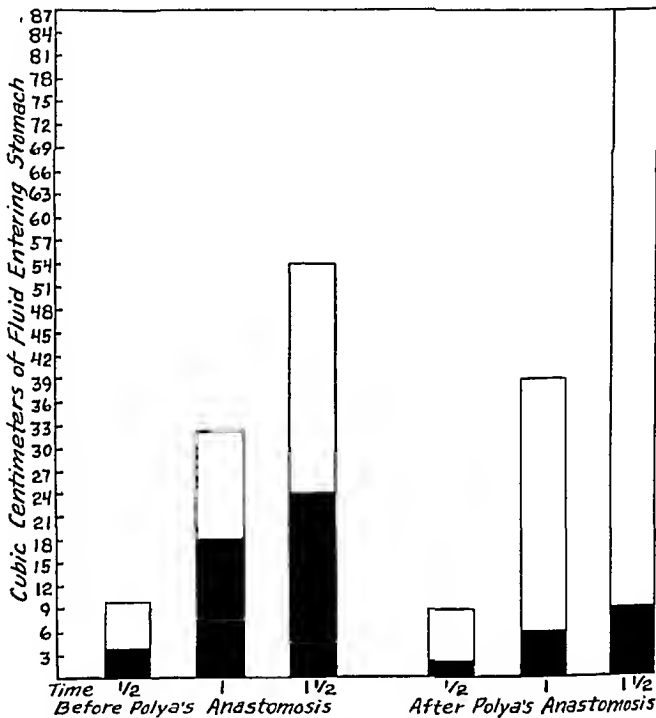


Fig. 4.—Chart showing the cubic centimeters of fluid per hundred cubic centimeters of test meal entering the stomach of dog D before and after partial gastrectomy with Polya's anastomosis. The findings are indicated as in figure 1.

was removed. Both of the foregoing types of pouch are partially denervated, since the stomach has been cut across and many of the nerve fibers coming into it from above have been severed.

The two following kinds of pouch retain their nerve supply, but the continuity of the gastro-intestinal tract is interrupted and fluids were given by hypodermoclysis. Both of these types of pouch were made in two stages, so that the lower stump of the stomach would be healed before the second stage was done, and the studies, which were begun the next day, would not be complicated by hemorrhage from an unhealed suture line. In one type, which was to be used as a control, the stomach was separated from the duodenum at the pylorus, both stumps were closed and gastrojejunostomy was performed with a small stoma. At the second operation, about two weeks later, the opening in the jejunum was closed, and the opening in

the stomach was brought out through a stab wound as a gastrostomy opening. The other type of pouch was prepared in a like manner, except that the pyloric end of the stomach was also resected at the first operation. In one of these dogs a nonleaking fistula of the duodenum was also made, Mann's method being used, and the dog was given food through the fistula.

The meat extract meal was introduced into the pouch through the gastrostomy opening, fractional samples were removed every half-hour for two hours, and acid chloride and phenol red determinations were made on the original meal and each of the samples. The phenol red was used in order to correct for dilution of the meal by mucus secreted by the stomach.

In figure 6 we show the total quantity of acid chloride secreted by the pouches and corrected for dilution. Dog E had a partially denervated pouch with the pylorus intact. Dogs F and G had similar pouches with the pylorus removed. Dogs H, I and J had nondenervated pouches with the pylorus intact, and dogs K, L and M had nondenervated pouches without the pylorus.

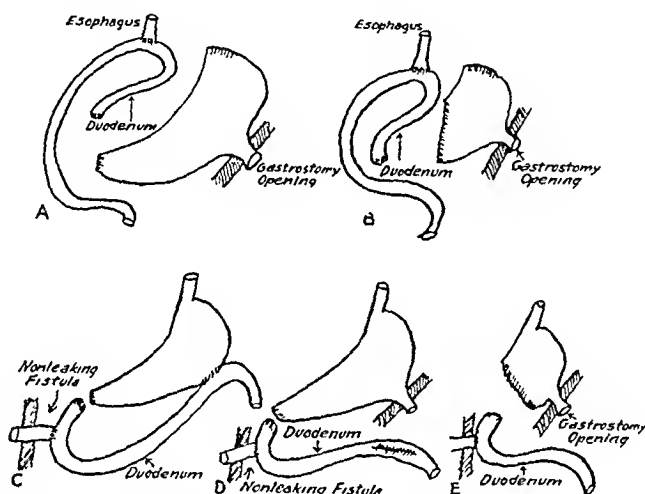


Fig. 5.—Diagrams of the types of whole stomach pouches described in the text. *A* shows a partially denervated pouch with pylorus; *B*, a partially denervated pouch without a pylorus; *C*, a nondenervated pouch with a pylorus, after the first stage of the operation; *D*, a nondenervated pouch with a pylorus, after the second stage of the operation, and *E*, a nondenervated pouch without a pylorus, after the second stage of the operation.

The reduction in the amount of acid secreted in the pouches without a pylorus is so pronounced as to require no comment. We believe that these experiments demonstrate that dilution and neutralization of acid in the stomach by regurgitated intestinal fluids are not a major factor in bringing about the lowered acidity after partial gastrectomy but that the pylorus is a link in the mechanism which causes the fundus to secrete acid. Whether this mechanism is a humoral or a nervous one our experiments do not as yet enable us to say. It will be noted that in none of the experiments has complete anacidity been produced, nor is this to be expected, since we have dealt only with the intragastric

factor. There are stimuli carried to the stomach through the vagus nerves, and there are stimuli arising in the intestine after the ingestion of a meal, both of which cause the secretion of acid by the stomach and neither one of which was affected by partial gastrectomy. Further studies which we have in progress are concerned with these other phases of gastric secretion and will be reported later.

CONCLUSIONS

1. Comparative studies on dogs on which partial gastrectomy and gastroduodenostomy have been performed show about the same total amount of fluid entering the stomach, but after partial gastrectomy the acid constituent of this fluid is diminished.

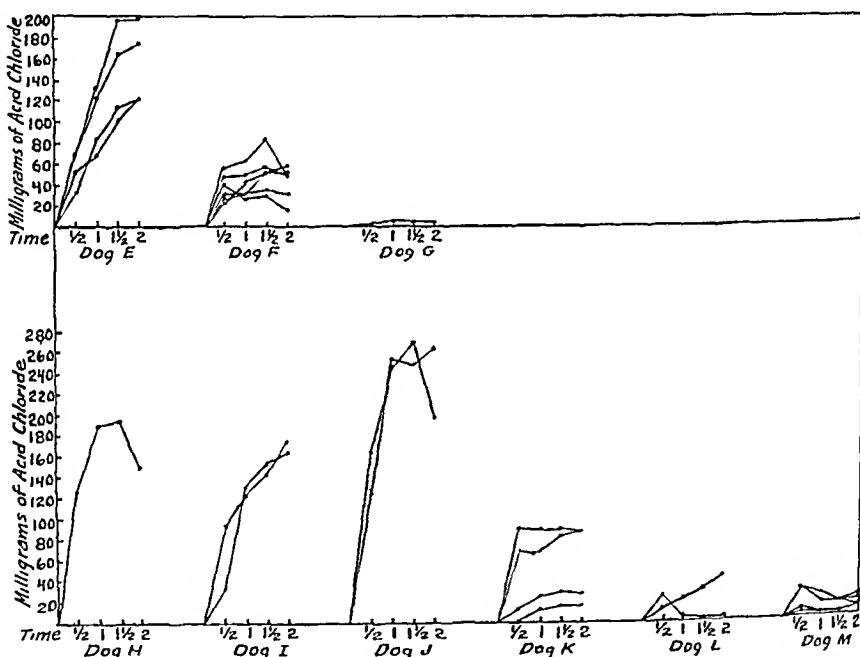


Fig. 6.—Curves showing the total amount of acid secreted by the pouches at intervals of one-half hour, expressed in milligrams of acid chloride. Dog E had a partially denervated pouch with the pylorus intact; dogs F and G had similar pouches with the pylorus removed. Dogs H, I and J had nondenervated pouches with the pylorus intact; dogs K, L and M had similar pouches, but the pylorus had been removed.

2. Studies on whole stomach pouches with and without the pylorus indicate that removal of the pylorus causes a failure of the fundic portion of the stomach to secrete the normal amount of acid.

3. The reduced acidity found after partial gastrectomy is due primarily to the loss of some stimulus arising in the pylorus and not to dilution and neutralization of the acid in the stomach by regurgitated intestinal fluids.

SPONTANEOUS RUPTURE OF THE NORMAL SPLEEN

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AND

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Reported cases of spontaneous rupture of the normal spleen have been appearing in the medical and surgical literature with ever increasing frequency in the past few years. With the exception of Susman's¹ work in 1927, no really critical study has been undertaken to evaluate the cases reported, with the ultimate aim of evolving a rational theory to explain such phenomena. As the subject is one which does not lend itself to experimental study, all work done on it must of necessity be inferential. For this reason, we have made an exhaustive study of the literature, searched out reports of all possible cases, analyzed each case carefully, including one of our own, discarded any which even remotely did not appear to be authentic, and from the remaining genuine cases have developed a concept which, we believe, can explain such phenomena.

That a normal spleen can rupture spontaneously has been the subject of considerable controversy. Ledderhose² and Foucault³ have maintained that spontaneous rupture can occur only in a diseased spleen. Sidney Smith⁴ has assumed a similar attitude. However, microscopic examination of the spleen in all reported cases in which sections of the spleen were taken for study has failed to show any demonstrable pathologic process. The conjecture has been advanced by some that the supposedly normal spleen is only apparently healthy, that the spleen is abnormal at one area only, which area is the point of rupture, and that all evidence of pathologic change is destroyed by the disintegration asso-

From the Department of Pathology, the Beth-El Hospital, Brooklyn, and the office of the chief medical examiner of the city of New York, Dr. Thomas A. Gonzales, acting chief medical examiner.

1. Susman, M. P.: Spontaneous Rupture of the Spleen, *Brit. J. Surg.* **15**:47 (July) 1927.

2. Ledderhose, G., in Billroth, C. A., and Luccke, G. A.: *Deutsche Chirurgie*. Stuttgart, 1890, pt. 45b, p. 147.

3. Foucault: Les ruptures spontanées de la rate et leur traitement, *J. de méd. de Bordeaux* **55**:1138, 1925.

4. Smith, S.: *Forensic Medicine*, ed. 4, London, J. & A. Churchill, Ltd., 1934.

ciated with the rupture. However, it is hard to conceive that an organ as notorious as is the spleen for the widespread dissemination of any pathologic process in it would have all preexisting pathologic process wiped out by rupture. Some microscopic abnormality would undoubtedly be left, either in some unruptured portion of the organ or in close proximity to the point of rupture. Wohl⁵ has shown that histologically the spleen ages early. Fifty per cent of spleens from persons 36 years of age show thickening and hyalinization in the malpighian bodies and capsule as well as thickening of the blood vessels. If these early degenerative changes were causative in splenic rupture, one would expect a greater incidence of this condition as well as a greater incidence with increasing age. However, both of these premises are untenable, as spontaneous rupture is a comparative rarity, and in the reported cases the frequency of this condition does not follow the age distribution to be expected if this were so. Another objection raised against spontaneous rupture is the possibility of some remote, perhaps forgotten or unnoticed, trauma. Here again, we have thoroughly scanned the literature and discarded all cases in which even the slightest suggestion of a traumatic history was reported. After such elimination, there still remained cases in which the traumatic element was entirely absent. We are therefore forced back to the conclusion that spontaneous rupture does occur in the normal spleen—normal in both gross and microscopic structure.

REVIEW OF THE LITERATURE

The first reported case, that of Atkinson⁶ in 1874, must be regarded as of doubtful authenticity. Although there was no history of trauma and splenic rupture was noted at autopsy, the author's description leaves one in confusion. Just what he implied by "lower portion of spleen disintegrated and in a state of muddy pulp" is highly problematic and forces one to question the normalcy of the spleen before rupture. From the description, it is highly conceivable that the spleen was the seat of a preexisting leukemic or infectious process.

The next reported case, that of Skerritt⁷ in 1878, must also be regarded with considerable doubt. Here again, although no history of trauma was elicited and postmortem examination showed splenic rupture, no information as to the gross and microscopic appearance of the organ was given by the author. In the absence of such data it is impossible to pass any opinion as to the normalcy of the spleen before rupture.

5. Wohl, M. G.: Spontaneous Rupture of the Spleen, *Ann. Surg.* 82:246 (Aug.) 1925.

6. Atkinson, E.: Death from Idiopathic Rupture of the Spleen, *Brit. M. J.* 2:403, 1874.

7. Skerritt, E. M.: Spontaneous Rupture of the Spleen, *Brit. M. J.* 1:641, 1878.

Shorten's⁸ case must be considered authentic in spite of a history of abdominal injury eighteen months previous to rupture of the spleen. In this instance the finding of a spleen which was both grossly and microscopically normal, as well as the absence of any adhesions to prove a possible previous injury or tear, must negate the importance of the past history of trauma.

The case presented by Connors⁹ and the two cases described by Metcalfe and Fletcher¹⁰ were incompletely reported. The authors failed to give any detailed description, either gross or microscopic, which would establish the previous normalcy of the organs they found ruptured.

Capecchi's¹¹ case must be regarded with some doubt in view of the absence of pathologic studies. The author could not attribute the slight splenomegaly that he found to any cause. However, there is no need to do so, for enlargement per se may be caused by acute congestion, and congestion is part of the picture of spontaneous splenic rupture.

In Stretton's¹² case, although the patient did not give a direct history of trauma, she did give a history of coitus just previous to the rupture. The author suggested the possibility of excessive violence in coitus as an etiologic factor. The element of trauma is thus indirectly introduced into this case.

Again, in Susman's¹ case, despite the absence of a history of direct external injury, one must not lose sight of the fact that the patient bent down to lift a heavy object. It is conceivable that the sudden muscular contraction of the abdominal wall incident to this task might have operated in a fashion similar to external trauma and produced the rupture. At any rate, here again, a spleen both grossly and microscopically normal was found.

In Rhame's¹³ case of rupture of the spleen in a young man the history was irrelevant and no significant pathologic changes were observed. The ruptured organs showed some thickening and hyalinization of the capillaries of the malpighian corpuscles and a recent thrombus in the veins at the root of the spleen without any changes in the walls of the blood vessels. The author, however, was skeptical as to the

8. Shorten, W. W.: Apparent Spontaneous Rupture of a Normal Spleen, *Brit. M. J.* 2:844 (Dec. 27) 1919.

9. Connors, J. F.: Ruptured Spleens, *Ann. Surg.* 74:1 (July) 1921.

10. Metcalfe, R. F., and Fletcher, L. Z.: Ruptured Spleen, *Ann. Surg.* 75:186 (Feb.) 1922.

11. Capecchi, E.: Spontaneous Rupture of the Spleen, *Policlinico (sez. prat.)* 32:665 (May 11) 1925.

12. Stretton, J. L.: Abdominal Cases Illustrating Important Surgical Principles, *Brit. M. J.* 1:901 (May 29) 1926.

13. Rhame, J. S.: Spontaneous Rupture of the Spleen with Venous Thrombosis, *Ann. Surg.* 88:212 (Aug.) 1928.

occurrence of spontaneous rupture and advanced the view that the existing pathologic process might have been wiped out at the time and site of rupture. This view has already been discussed.

The case reported by Underwood¹⁴ presents several elements of doubt. Although the spleen was found to be microscopically normal, there were old adhesions posteriorly and at the right upper pole, as well as a slight degree of fibrosis and hyaline degeneration of the blood vessels, together with some pigmentation. These factors, especially the old adhesions and the pigmentation, suggest some previous pathologic process, although what are loosely and commonly called adhesions are often aberrant peritoneal reflections, having none of the pathologic significance implied by the term "adhesion."¹⁵

Harvey's¹⁶ case, in which the spleen was slightly larger than normal and microscopy showed no abnormalities, is unquestionably authentic. Here also, the author noted a few adhesions at the upper pole, which, as explained before, might well have been some aberrant peritoneal reflections.

Bailey's¹⁷ case meets all the requirements for the spontaneous rupture of a normal spleen in regard to both the history and the histologic picture. Yet the author, in spite of a carefully taken history, expressed the belief that there may have been an element of trauma that was either forgotten or overlooked by the patient.

In Byford's¹⁸ presentation, microscopy of the spleen showed an increase in fibrous elements, with marked thickening and hyalinization of some of the blood vessels. As has been pointed out before, Wohl has shown that this is a normal occurrence in a large proportion of spleens and is not to be taken as evidence of a previous pathologic process. Byford's case must therefore be considered genuine.

Nixon,¹⁹ in reporting his case, mentioned only slight enlargement of the spleen but failed to give any gross or microscopic description of the organ. This is due to the fact that at operation mattress suturing of the spleen and not splenectomy was done and that after the death of the patient autopsy was not performed. There was no history of trauma.

14. Underwood, W. E.: Spontaneous Rupture of the Spleen, *Brit. M. J.* **1**:1118 (June 22) 1929.

15. Stockard, C. R.: The Trend of Morphology, *Science* **69**:363 (April 5) 1929.

16. Harvey, T. W., Jr.: Spontaneous Rupture of the Spleen, *J. A. M. A.* **93**: 987 (Sept. 28) 1929.

17. Bailey, H.: Spontaneous Rupture of the Normal Spleen, *Brit. J. Surg.* **17**: 417 (Jan.) 1930.

18. Byford, W. H.: Spontaneous Rupture of the Normal Spleen, *Arch. Surg.* **20**:232 (Feb.) 1930.

19. Nixon, P. I.: Spontaneous Rupture of the Normal Spleen, *J. A. M. A.* **96**:1767 (May 23) 1931.

Demel's ²⁰ case must be excluded because it introduces the questionable factor of a retrograde thrombosis secondary to an embolic process. It is, furthermore, too vaguely described from the point of view of this paper.

In Black's ²¹ case the spleen again showed some thickening and hyalinization of the central arteries. This finding, as shown before, is to be disregarded and the case accepted as genuine.

In Dardinski's ²² case, in addition to spontaneous rupture of a normal spleen, there was an irregularly enlarged nodular liver (primary malignant hepatoma of the liver). The author expressed the belief that the rupture was due to an increase of pressure in the organ as a result of a damming back of blood from the liver. That the local congestion played a part in the rupture is possible, but it must be remembered that such congestion, caused by obstruction to the splenic venous circulation either within the liver or in the portal vein (Nobel and Wagner ²³) or found even in association with severe cardiac failure, is a common occurrence in spleens that do not rupture. This suggests that other factors not discussed by the author were operative in this case.

Kaspar ²⁴ reported an interesting case in a young man and suggested that an unusual digestive hyperemia of the spleen might have had something to do with the rupture.

Halliwell ²⁵ presented an interesting case in which the splenic pedicle was unusually long. He took exception to the view that there might have been a forgotten injury in his patient and pointed out that although the spleen has better protection than the intestines or the kidneys against possible trauma, yet it alone ruptures spontaneously.

Bohler's ²⁶ case presents the same difficulty as does Susman's.¹ Here also there was a history of the patient's bending to lift a heavy object, with the possibility of the sudden muscular contraction and increased intra-abdominal pressure acting as a traumatic element.

20. Demel, V. C.: Di un caso di rottura spontanea della milza, *Riforma med.* **47**:522, 1931.

21. Black, J. M.: Spontaneous Rupture of the Spleen, *Brit. J. Surg.* **20**:526-(Jan.) 1933.

22. Dardinski, V. J.: Spontaneous Rupture of an Apparently Normal Spleen, *J. A. M. A.* **99**:831 (Sept. 3) 1932.

23. Nobel, E., and Wagner, R.: Die Thrombose und Phlebitis der Milzvene im Kindesalter („Milzvenenstenose“), *Ergebn. d. inn. Med. u. Kinderh.* **45**:1, 1933.

24. Kaspar, M.: Ein Fall von Spontanruptur der gesunden Milz, *Beitr. z. klin. Chir.* **156**:97, 1932.

25. Halliwell, A. C.: Spontaneous Rupture of Normal Spleen, *Brit. M. J.* **1**:919 (May 27) 1933.

26. Bohler, E.: Eclatement du hile de la rate au 7e mois de la grossesse, *Bull. Soc. d'obst. et de gynéc.* **22**:707 (Oct.) 1933.

Abell²⁷ neglected to give the results of the microscopic examination in the case that he reported.

The splenomegaly in the case reported by Smith, Morrison and Sladden²⁸ was found to be due to an intense congestion of the sinuses and not to any intrinsic pathologic process in the spleen.

Lundell²⁹ and Dahle³⁰ each reported an unquestionably genuine case, as did Basso,³¹ in a patient in whom autopsy revealed an unsuspected spontaneous rupture of a normal spleen.

In Burnett and McMenemey's³² case the slight splenomegaly found was shown by microscopy to be due solely to congestion.

In the last reported case, that of Young,³³ there were no doubtful features, and examination of the spleen suggested that some violent internal force, such as increasing engorgement of blood, may have been at work to cause explosive tears in the capsule.

REPORT OF A CASE

The case we are presenting is interesting for two reasons: In the first place, it is a genuine case of spontaneous rupture of a normal spleen, and in the second place, it casts some light on what we believe to be the mechanism of spontaneous rupture.

History.—A white woman aged 29, thirty-two hours prior to her admission to the hospital, had a sudden nonradiating pain in the left upper quadrant of the abdomen and in the left flank. The pain was not associated with chills, urination or hematuria. It remained localized to the left upper quadrant and left flank for the next twenty-four hours, but with lessened intensity. Just previous to her admission to the hospital the patient complained of some epigastric distress and vomited twice. She was seen by an ambulance surgeon at home but was not hospitalized until four hours later, when she was found in shock. Subsequent questioning of the physician who saw the patient before the ambulance surgeon, as well as of the latter, failed to disclose even the slightest suggestion of a history of trauma. Both had inquired closely on this specific point; both stated, further,

27. Abell, I.: Wandering Spleen with Torsion of the Pedicle, *Ann. Surg.* **98**: 722 (Oct.) 1933.

28. Smith, A. H. D.; Morrison, W. J., and Sladden, A. F.: Spontaneous Rupture of the Spleen in a Pregnant Woman, *Lancet* **1**:694 (April 1) 1933.

29. Lundell, G.: Ueber spontane Milzruptur, *Acta chir. Scandinav.* **75**:547, 1934.

30. Dahle, M.: Ruptur von normales Milz ohne bekannte Ursache-Spontanruptur? *Acta chir. Scandinav.* **75**:519, 1934.

31. Basso, R.: Rottura spontanea della milza nel decorso di un'angina, *Gior. veneto di sc. med.* **8**:275 (March) 1934.

32. Burnett, E. C., and McMenemey, W. H.: Rupture of the Normal Spleen in Pregnancy, *Brit. M. J.* **1**:1122 (June 1) 1935.

33. Young, R. D.: Spontaneous Rupture of a Normal Spleen, *Ann. Surg.* **101**:1389, 1935.

that there was not the slightest suggestion even of unusual physical activity at or before the onset of symptoms for at least three or four days before the patient was seen.

Physical Examination.—The patient was markedly anemic, with extreme pallor of the lips and finger-tips. All mucous membranes showed extreme pallor. She was semicomatose, with a respiratory rate of 30 and a pulse rate of 140, the beat being thready in character. The head and neck showed no abnormalities. The lungs were clear. The heart sounds were regular, with a rate of 140, and were of poor quality and without any bruits. The abdomen was distended over the lower portion, particularly the right side. There was tenderness in the epigastrium in both upper quadrants and in the left lumbar region. A positive Murphy sign was found on the left side. The spleen was palpable 2 fingerbreadths below the costal margin. The edge of the liver was not felt. There was no area of dullness in the flanks. The extremities were normal. The temperature was 99 F. Examination of the blood showed a count of 17,000 white cells, of which 80 per cent were polymorphonuclears and 20 per cent were lymphocytes. The hemoglobin content was 58 per cent (Sahli).

Tentative diagnoses of pancreatitis and ectopic gestation were made, the latter in spite of the fact that the patient's last menstrual period occurred ten days before admission to the hospital. The surgical staff was called in consultation, and internal hemorrhage was considered the cause of the shock. Before antishock measures could be instituted, the patient died.

Autopsy.—Examination was performed one-half hour after death. The peritoneal cavity was filled with much blood and clots, chiefly in the pelvis and the left gutter. The spleen measured 17 by 9.5 by 5 cm. and weighed 385 Gm. It was firmer than normal. The capsule was tense and blue. The organ lacked attachment to the inferior diaphragmatic surface above (phrenicolienal ligament). It was bent on itself to about a right angle, the apex of the angle being at the midportion of the convex surface. Here, there was a transverse fissure 3.5 cm. in length and 0.8 cm. in depth. A point 0.5 cm. in front of its anterior end was the seat of a superficial rupture (possibly through a small vessel) which was 0.3 cm. long. It bled freely on slight pressure on the surrounding tissue and was surrounded by a recent blood clot. The hilus contained a smooth-surfaced, bluish, well defined mass, which was soft and rubbery, measured 5 cm. in diameter and was somewhat irregular; it could not be dissociated from the body of the organ. The mass was covered by large, moderately firm adherent clots. It consisted of thrombosed, dilated hilar veins, surrounded by edematous hemorrhagic tissue. The thrombi were lamellated, extending for a short distance into the intraperitoneal vessels and for 2 cm. into the main vessel, being softer, lighter red and of apparently more recent origin in the latter location. The intima of all branches was smooth and glistening; the thrombi were nowhere adherent to it. The splenic artery coursed through the mass, its lumen and those of its branches being patent throughout. The parenchyma presented a picture of extreme congestion, none of the gross structure ordinarily seen being recognizable. The splenic flexure of the colon had numerous fibrinous adhesions to the lateral abdominal wall. The body and tail of the pancreas from just to the left of the midportion were only loosely attached to the posterior abdominal wall by a mesentery-like fold of areolar tissue. This part of the pancreas was easily mobile but was not twisted or displaced. Posteriorly, this portion of the pancreas was covered by a smooth, glistening surface. More laterally toward the right, this surface disappeared, as did the loose mesentery-like structure of areolar tissue, as the posterior pancreatic surface

became densely adherent to the posterior abdominal wall. Toward the spleen, the tail of the pancreas became loosely attached to the spleen just below the hilus, the posterior pancreatic mesentery being lost in the densely hemorrhage-infiltrated tissue that surrounded the hilus. The spleen was loosely adherent to the splenic flexure, but no distinct ligamentous connection could be ascertained because of the extensive hemorrhage. The gastrosplenic ligament was heavily infiltrated with dark red clotted blood, and a similar infiltration covered the left lateral anterior surface of the pancreas. The omental bursa was devoid of blood and showed no gross anatomic changes; the foramen of Winslow was patent.

The rest of the autopsy showed nothing particularly abnormal. All the viscera were extremely pale and bloodless.

Microscopy of the spleen showed all the sinuses extremely distended with masses of well preserved erythrocytes, in such huge numbers that the intervening pulp was almost nowhere apparent, being represented by a few lymphocytes. No other changes were noted. Microscopy of the remainder of the organs showed nothing but severe anemia.

The anatomicopathologic diagnosis was: (1) acute posthemorrhagic anemia of the viscera, (2) acute intraperitoneal hemorrhage, (3) shock and (4) spontaneous, nontraumatic rupture of the spleen, intrasplenic congestion and hemorrhage and recent thrombosis of the splenic vein, mechanical (torsional?) and static.

. COMMENT

To understand the existing relations in the abdominal viscera in this case, it is necessary to review briefly the embryology of the spleen and pancreas and the disposition of the peritoneal folds as they change from the embryonic state to that found in adult life. Originally the peritoneum leaves the posterior abdominal wall in the midline and passes forward to encircle the vertically lying stomach as a double-layered mesentery, the dorsal mesogastrium. As the stomach becomes rotated toward the right and horizontal (its left lateral surface becomes its adult anterior surface, while the right lateral surface becomes its adult posterior surface), the dorsal mesogastrium is pulled toward the left. This process, coupled with the great overgrowth and redundancy of the dorsal mesogastrium, causes it to assume a U-shaped appearance, the hollow of the U facing toward the right behind the stomach, the hollow being the precursor of the adult lesser sac. Within the loose areolar tissue of the dorsal mesogastrium and between its two layers at or near the point of greatest convexity, the splenic anlage develops. It is at first entirely invested on all surfaces by peritoneum. By adhesion later of parietal peritoneal surfaces as the lateral bending of the dorsal mesogastrium continues, the peritoneal investment of the spleen leaves it at the hilus and passes over to the lateral border of the kidney. This reflection is brought about by the adhesion of the ventral peritoneal layer of the dorsal mesogastrium (originally its right leaf) to the posterior abdominal wall to form the dorsal surface of the retrogastric space, the left leaf of the dorsal mesogastrium, by its adhesion to the parietal peritoneum over the kidney and diaphragm, forming the adult

lienorenal and lienophrenic ligaments. At these points of adhesion, firm strands of connective tissue later develop between the serous surfaces. By adhesion of the dorsal mesogastrium to the splenic flexure, the colocolic ligament is formed in similar manner, while similar adhesion of the dorsal mesogastrium to the great omentum, transverse mesocolon and phrenic parietal peritoneum just caudad to the spleen forms the colicophrenic and costocolic supporting ligaments of the spleen. These changes occur during the second half of intra-uterine life.

Meanwhile, the pancreas has begun as an outbudding from the definitive duodenal portion of the embryonic intestine, pushing its way between the layers of the mesoduodenum. It then turns cephalad, pushing its way between the layers of the dorsal mesogastrium by the displacement of which, occasioned by the gastric rotation, it is brought backward against the posterior abdominal wall. At this juncture, its original posterior peritoneal investment, the reduplication of the original left lateral leaf of the dorsal mesogastrium, becomes adherent to and fused with that fold of dorsal mesogastrium reduplicated from the left lateral leaf and previously adherent to the posterior parietal peritoneum. The pancreas thus becomes fixed and virtually extraperitoneal, and the main splenic vessels, originally situated between two peritoneal layers in front of the pancreas, now, through the interposition of this organ and the subsequent fusion of the posterior peritoneal investment of this organ, is covered by peritoneum only anteriorly (Huntington³⁴).

If, therefore, this fusion, for whatever reason, fails to develop properly and completely, the pancreas in whole or in part remains, as it originally was, an intraperitoneal organ, and the usual splenic supporting ligaments fail to develop. Of these, the lienophrenic and the lienorenal ligament are probably the most easily affected, since it is in this lateral region that disturbances of adhesion of peritoneal surfaces would be occasioned by the neighboring pancreas. Situated as the pancreas is, posteriorly and rather remotely, the colicophrenic and the costocolic ligament are less apt to be disturbed in formation. Besides, these two structures are not intimately connected with or are not a part of the spleen and its investments and hence cannot limit its motion by tension. Directly they cannot limit its mobility except by resisting its advance in their direction, a force of doubtful importance when their thin elastic structure is considered.

That such must have been the state of affairs in this case is suggested by the loosely adherent attachment of the pancreas to the posterior abdominal wall, its attachment to the spleen and the presence of a rudimentary posterior pancreatic mesentery. This suggestion is further

34. Huntington, G. S.: *The Anatomy of the Human Peritoneum and Abdominal Cavity from the Standpoint of Development and Comparative Anatomy*, Philadelphia, Lea Bros. & Co., 1903.

strengthened by the absence of any semblance of a lienophrenic ligament. Such conditions, therefore, deprived the spleen of its major supports and afforded it greater mobility. It remained, however, as developmentally it must, closely connected with the stomach by the gastrosplenic ligament. With its physiologic mobility during digestion, hunger and other unusual causes, it is possible that the stomach, in its contractions, pulled the unchecked and unsupported spleen into unusual positions, causing recurrent, albeit temporary, passive congestion. It is not improbable to conceive of an excessive force so distorting the position of the spleen as to cause the congestion to become sufficient, especially if lasting for some time, to occasion subcapsular hemorrhage and subsequent capsular rupture, with the resulting clinical picture. In this connection, it must be remembered that the splenic circulation is an open one³⁵ and that it is therefore more liable to subcapsular hemorrhage. Alternatively, it may be that the recurrent displacement of the spleen, with the resulting changes in the course of the splenic vessels, especially at or near the hilus, produced a gradual thrombosis of the more labile vessel, the splenic vein. This may so have narrowed the venous lumen that a sudden excessive distortion brought about by a more extreme change in position may have caused a pronounced passive congestion, with subsequent subcapsular hemorrhage and capsular rupture. The recurrent abdominal pain and the at first gradual, then rapid, development of abdominal signs and symptoms, suggest that the process was not continuous but intermittent, the first phase being due to subcapsular hemorrhage, and the second, or shock, phase, to the capsular rupture and intraperitoneal hemorrhage. It is not necessary to assume, as is so frequently done with hemorrhages into ovarian cysts that are not of endometriotic origin, that the pedicle had been twisted, the hemorrhage brought about, and, before laparotomy or autopsy, the pedicle had become untwisted. In an organ the position of which is closely delimited and the vessels of which are rather rigidly fixed by surrounding tissues, positional changes less than pedicle torsion may be sufficient to slow the circulation and cause intraparenchymal congestion and hemorrhage, as was found in this case.

From the clinical and pathologic pictures, it is probable that some intra-abdominal (gastro-intestinal?) physiologic upset, with altered dynamic relations of the viscera, caused a partial recurring torsion of the spleen, with resulting thrombosis of the splenic vein and splenic parenchymal congestion of an extreme grade, which finally led to rupture, shock and death. The absence of the diaphragmaticocolic ligament and its reflection of the abdominal wall, the chief supports of the spleen

35. Maximow, A. A., and Bloom, W. A.: *A Textbook of Histology*, ed. 2, Philadelphia, W. B. Saunders Company, 1934.

(these are absent rarely—less than 2 per cent together³⁶), make this theory likely. Furthermore, the attachment of the splenic flexure of the large intestine and the upper part of the descending colon, together with the loose mesenteric attachments of the latter, suggest that the spleen may have been moved mechanically with them in some colonic physiologic disturbance.

Spontaneous splenic rupture is important from the medicolegal point of view. It is a well known fact that traumatic injuries of abdominal viscera may occur without external signs, cutaneous or muscular, of the inciting trauma.³⁷ Under such circumstances, a surgeon finding a ruptured spleen may be called on to attest its traumatic character.⁴ As we have pointed out, however, there exist genuine cases of nontraumatic, spontaneous splenic rupture. Such testimony must, therefore, be given with caution and only when a clearcut history of trauma is obtained.

CLINICAL FEATURES

An analysis of the clinical features of these cases reveals some interesting facts:

1. Sex apparently plays no part in the picture. In the twenty-one genuine and seven dubious cases reviewed, the rupture occurred sixteen times in males and twelve times in females.

2. Age appears to play no part. The condition occurred twice in persons under 20 years of age, seven times in those between 20 and 30, six times in those between 30 and 40, seven times in those between 40 and 50 and five times in those between 50 and 60. The condition appears to be fairly evenly distributed throughout the various age periods.

3. In five of the cases in which no intrinsic lesions of the stomach or gallbladder could be detected there was a well established history of epigastric distress related to meals.

4. In five cases the onset of attack occurred shortly after eating or drinking.

5. The site of rupture was extremely variable, showing no decided predilection for any site. The lower and upper poles, the convex and concave surfaces, the hilus and the splenic notch were involved with equal frequency.

³⁶ Cunningham, D. J. *Text-Book of Anatomy*, ed. 5, New York, William Wood & Company, 1925. Huntington³⁴

³⁷ Vance, B. M. Subcutaneous Injuries of the Abdominal Viscera. *Anatomic and Clinical Characteristics*. *Arch. Surg.* **16**:631 (March) 1928.

6. Vomiting occurred in only twelve of the cases. (Trendelenburg³⁸ claimed that this is a constant sign in rupture of the spleen.)

7. Shock occurred in only fifteen cases.

8. Pain in the left shoulder, although supposed to be pathognomonic of splenic rupture, occurred in only three cases. Pain in the right shoulder occurred in only one case.

SUMMARY

A case of spontaneous rupture of a normal spleen is reported. The embryogenesis of the spleen and its peritoneal supports is reviewed. The physiologic and anatomic conditions making possible spontaneous rupture are described and discussed. The literature is critically reviewed; reports of twenty genuine cases and seven questionable cases are collected. Some interesting clinical features are noted.

It is suggested that future cases be studied carefully from the point of view of physiologic dynamics of the abdominal cavity and the anatomic relations of the splenic and pancreatic peritoneal reflections.

The medicolegal significance of this condition is pointed out.

Dr. Benjamin Kogut, attending surgeon at the Beth-El Hospital, gave us permission to use the clinical data in the case reported here.

38. Trendelenburg, in discussion on Finsterer, H.: *Zur Diagnose und Therapie der stumpfen Bauchverletzungen*, Wien. med. Wchnschr. 68:1217, 1918.

PRURITUS ANI

HISTOLOGIC PICTURE IN FORTY-THREE CASES

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AND

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Seldom may one find a disease so little understood as pruritus ani. There is great dissension in regard to its cause. The variety of remedies which have been offered proves that nothing has been produced resembling a cure.

DIRECT AND INDIRECT PRURITUS

Montague¹ distinguished two types of pruritus, direct and indirect. The latter is called by others essential or idiopathic pruritus.

In the direct type of pruritus, local anal diseases such as fistulas, fissures, ulceration of the anus and rectum, polyps, papillae and hemorrhoids have been given as causes. In the indirect type of pruritus, Montague regarded the itching as a referred sensation caused by disorders in distant organs, i. e., the stomach, gallbladder and appendix and other organs. Montague expressed the belief that whenever a viscus is the seat of a disease a stream of afferent stimuli is generated and transmitted to the central nervous system. The irritant stimulus is referred, not to its true source, but to the skin of the anal region.

Bacteria and fungi, pediculi and pin worms have been mentioned frequently as etiologic factors. Various constitutional disorders, such as uremia, gout, diabetes and rheumatism, have been blamed for the production of pruritus. In a certain percentage of cases the condition has been attributed to allergy.

In the face of all these divergent theories, it may be truthfully said that the etiology of this distressing condition is not known.

About thirteen years ago, Lockhart-Mummery² wrote that histologic examination of pruritic skin may solve some day the mystery of pruritus ani. In the literature we could, however, find only two such studies. Montague,¹ in his book on pruritus, described an acute or subacute

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1. Montague, J. F.: *Pruritus of the Perineum*, New York, Paul B. Hoeber, Inc., 1924.

2. Lockhart-Mummery, L.: *Diseases of the Rectum and Colon*, New York, William Wood & Company, 1923.

exudative dermatitis, with lichenification and kraurosis as possible end-results. In Buie's book,³ Montgomery reported the results of histologic study in five cases of pruritus ani. He expressed the belief that the changes in the skin in cases of pruritus ani correspond closely to those seen in cases of neurodermatitis.

MATERIAL

Our present paper is based on the clinical and histologic studies of 43 cases of anal pruritus, which were found among 386 patients with conditions of the rectum—an incidence of 11 per cent. There were 22 men and 21 women. No Negroes were in the group. While Montague¹ expressed the belief that there is no racial predisposition in pruritus ani, Taussig⁴ pointed out that he had hardly ever seen a Negress with pruritus.



Fig. 1.—First stage of pruritus of a few weeks' duration. There are redness and swelling of the skin, not only around the anus but also in the area extending to the coccyx.

No children were observed with true pruritus. Our youngest patient was 24 years old, and the oldest, a woman, was 76 years old. The average age of the men was 45.1 years, and of the women, 37.4 years.

ANAL LESIONS IN PRURITUS ANI

In our cases we made a histologic study of not only the specimens removed from the pruritic zone, but also every surgical specimen obtained from the anal canal. We hoped that the anal canals of patients with pruritus might differ from those of patients without pruritus. The great majority of our patients with pruritus presented one or more pathologic conditions in the anal canal. They were, in the order of

3. Montgomery, in Buie, L. A.: *Proctoscopic Examination and the Treatment of Hemorrhoids and Anal Pruritus*, Philadelphia, W. B. Saunders Company, 1931.

4. Taussig, F. J.: *Leukoplakic Vulvitis and Cancer of the Vulva*, *Am. J. Obst. & Gynec.* 18:472, 1929.



Fig. 2.—Intra-epithelial edema in the first stage of pruritus.



Fig. 3.—First stage of pruritus with vesicle formation.

frequency: hemorrhoids, infection of the anal ducts, inflammation and hypertrophy of the papillae, fissures and fistulas.

By special nerve stains, our attention was attracted to a large number of myelinated nerves which were running to the tip of the anal papillae, at the mucocutaneous line. In the tip of the anal papillae, almost without exception, Meissner's tactile corpuscles were found lying beneath the epithelium. The presence of these tactile bodies explains the extreme sensitivity of the anal papillae. It is possible that inflammations, which are so common near the mucocutaneous line, irritate these nerve corpuscles and thus produce the sensation of itching.



Fig. 4.—Photomicrograph of the lesion in figure 3. A vesicle is shown in the epidermis.

Histologic study, however, of surgical specimens removed from the 343 patients without pruritus revealed that the pathologic picture of the anal canal of a patient with pruritus was not different from that of the anal canal of a patient without pruritus. Therefore anal lesions cannot be regarded as the essential cause of pruritus. This would conform with our clinical experience. Follow-up studies which we made in our series of cases revealed that radical removal of all anal lesions often will improve the condition of the patient markedly, but seldom will bring about a complete cure.

HISTOPATHOLOGIC PICTURE OF THE SKIN IN PRURITUS ANI

The cutaneous changes found in our 43 cases differed according to the duration of the pruritus. Our youngest patient, a 27 year old woman, complained of severest itching for five months; our oldest patient had symptoms for thirty-five years. While different histologic pictures may be present in the same specimen of skin, we believe, never-

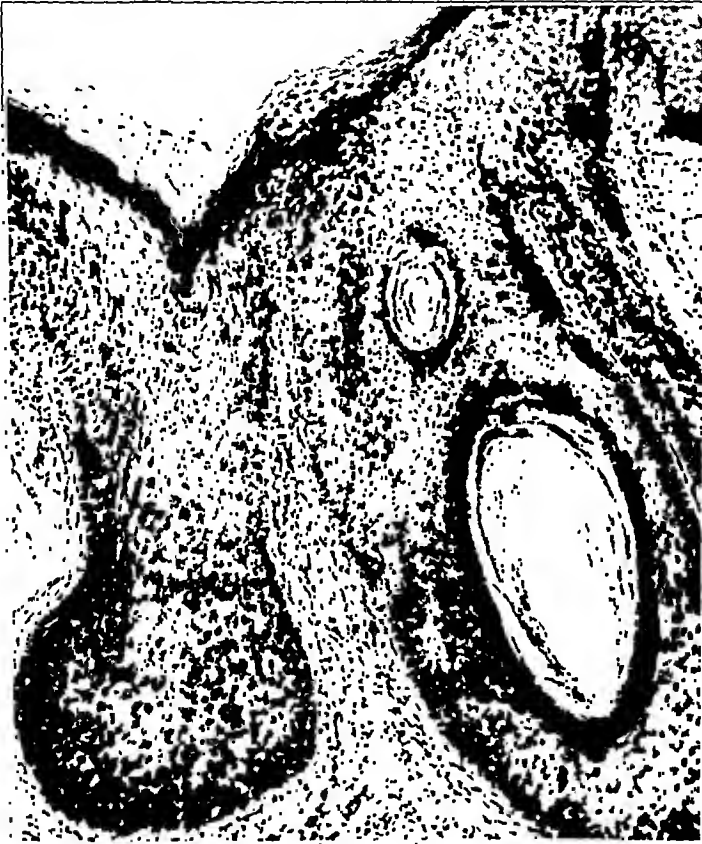


Fig. 5.—Second stage of pruritus. There are marked proliferation of the malpighian layer, and horny plugs in the hair follicle. The cells are undifferentiated.

theless, that pruritus ani runs a typical course, and we had no difficulty in classifying the cutaneous changes into four stages.

The first stage of pruritus shows evidence of exudative inflammation. The cells of the malpighian layer are markedly swollen, the structure of the protoplasm is entirely destroyed and a large clear space is found. The nucleus is compressed and pushed to the periphery of the cell body. It has the shape of a half-moon. The intercellular bridges are not recognizable. In the corium, dilatation of blood and lymph vessels is evident, and there is perivascular infiltration with lymphocytes, plasma

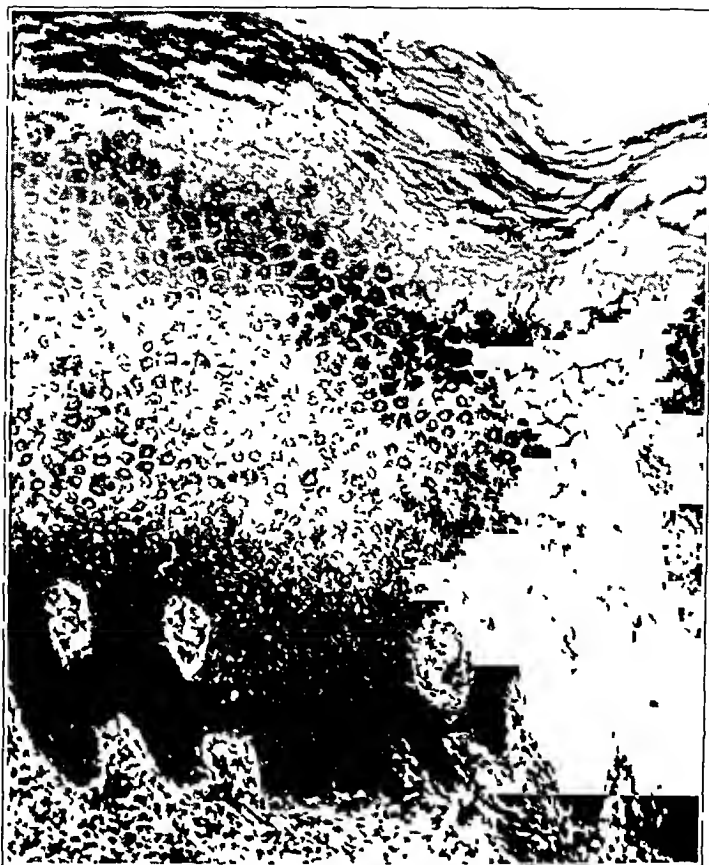


Fig. 6—Second stage of pruritus There is hyperkeratosis of the surface epithelium

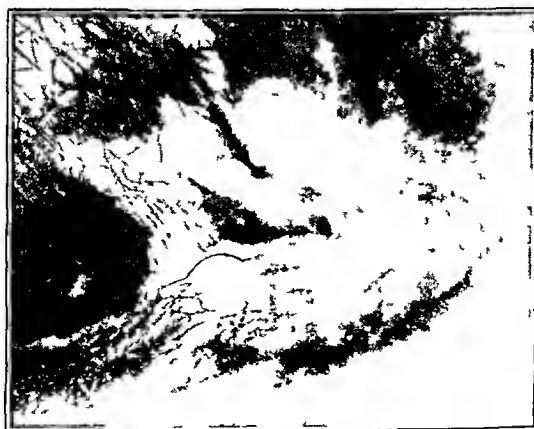


Fig. 7—Third stage of pruritus The skin is thin and dry and without hair and pigment

cells and occasional leukocytes. In a few cases exudate has collected in the upper layers of the epidermis and may form vesicles protruding over the surface.



Fig. 8—Third stage of pruritus. There are marked atrophy of the surface epithelium and the sebaceous glands and loss of hair.



Fig. 9—Fourth stage of pruritus. Torpid ulcers are seen in the atrophic skin surrounding the anus

The second stage of pruritus is characterized by epithelial hyperplasia. There is marked thickening of the epidermis. The rete pegs

are elongated and separated by narrow papillary bodies. The cells of the malpighian layer are deeply stained; they appear unripe and less differentiated than in normal skin. Often mitotic figures are present. In many cases the epidermal cells form either branching strands, growing into the corium or broad cell masses obliterating the papillary bodies. Marked cellular proliferation is also observed in the walls of hair follicles. Strands of young, undifferentiated cells are growing from the outer sheaths of hair follicles into the surrounding connective tissue. In many instances these proliferative areas have a definitely atypical appearance.

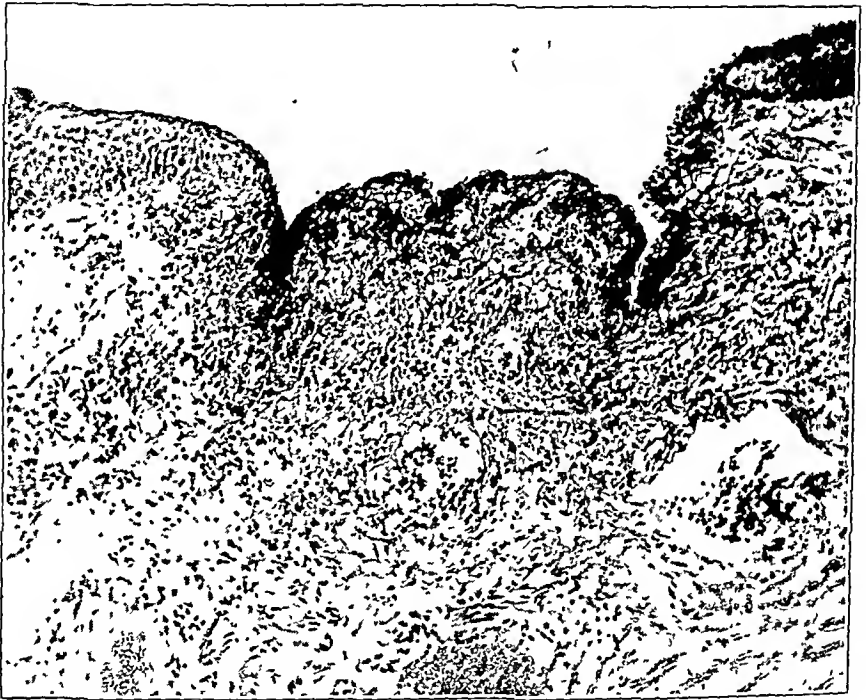


Fig. 10.—Section of pruritic skin with an ulcer. There is absence of a vigorous defense reaction.

The stratum corneum of the epidermis is also much thicker than normal. The ostium of hair follicles is plugged with hornified material. The same material is found in the ducts of sebaceous glands.

In the third stage of pruritus, atrophy of the epidermis and especially of the hair follicles and sebaceous glands is found. The surface epithelium is only a few cell layers thick, the hair follicles are distended by horny plugs and the sebaceous glands either are completely missing or consist only of undifferentiated cells which do not show evidence of secretory activity.

The fourth stage of pruritus is characterized by multiple epithelial defects. Excoriations, deep fissures and shallow ulcers are found. In some epithelial defects, leukocytic infiltration and marked edema are observed, apparently due to secondary bacterial invasion; more often, however, no vigorous defense reaction of the tissue is recognizable, and most of the ulcers look torpid.

Our observations coincide, in the main, with Montague's and especially with Montgomery's descriptions. Pruritus ani has, in our opinion, a definite histologic picture. Never have we seen these cutaneous changes in patients with disease of the rectum without pruritus.

COMMENT

Does the histologic picture of pruritus ani throw some light on the etiology of this condition? There is nothing in our observations which would suggest a bacterial or parasitic cause. We shall not deny that certain bacteria or fungi may complicate pruritus, but in the early stages in our cases no histologic evidence of bacterial or parasitic infection was present. Neither were the results of our microscopic examinations in harmony with the theory that pruritus is an allergic disease; and the neurogenic theory of pruritus also seems unwarranted in the light of our observations. We feel, furthermore, justified in disagreeing with those who believe that inflammatory lesions of the anal canal and hemorrhoids are responsible for pruritus. There was no difference between the pathologic picture of the anal canals of persons with pruritus and that of persons without pruritus.

In studying the cutaneous changes in cases of pruritus ani, we were reminded again and again of the histologic pictures described in cases of chemical dermatitis. Hydrops of the epidermis cells, irregular proliferation of the stratum mucosum and of the hair follicles, hyperkeratosis with plugging of the hair follicles and atrophy of the sebaceous glands are changes characteristic of dermatitis due to chemical irritants. The four stages which we have seen in pruritus i. e., (1) exudative inflammation, (2) epidermoid proliferation, (3) atrophy of the epidermis and sebaceous glands and (4) epithelial defects, can be produced in the skin of rabbits and mice by certain chemical substances which, in various pathologic conditions, are present in the human feces. We believe that besides other hydrocarbons, skatole may be the responsible agent, because Stoeber and Wacker⁵ were able, by the injection of skatole into the rabbit, to produce the same cutaneous changes which we have described in pruritus.

5. Stoeber, H., and Wacker, L.: Ein weiterer Beitrag zur Erzeugung atypischer Epithelwucherungen mit Eiweissfaeculnisprodukten. München. med. Wchnschr. 57:947, 1910.

Skatole, a methyl indole, is a derivative of protein and is formed in the intestines from tryptophan by the action of anaerobic bacteria. While skatole is absent in the stool of healthy children and also in the stool of most adults, Herter⁶ found excessive amounts in the feces of patients suffering from mental despression and anemia and especially from chronic intestinal disorders. These conditions are, according to Montague, often associated with pruritus. In healthy children, on the other hand, true pruritus is unknown.

SUMMARY

The histologic picture in 43 cases of pruritus is not in accord with the theory that bacterial or fungus infection is the cause of pruritus. Allergy and neurogenic factors can also be excluded as etiologic factors in the light of our microscopic observations. The results of our studies suggest as the underlying cause of pruritus and a chemical dermatitis. In pathologic conditions, the human feces contain substances which are known to produce the same cutaneous changes which we have observed in pruritus.

Follow-up studies which we made in our cases of pruritus revealed that radical removal of all lesions in the anal canal will improve the condition of the patient but will not bring about a complete cure. There is no difference between the pathologic picture of the anal canals of patients with pruritus and that of patients without pruritus. Anal lesions cannot be regarded as the essential cause of pruritus.

6. Herter, C. A.: The Occurrence of Skatole in the Human Intestines, *J. Biol. Chem.* 4:101, 1908.

REFLEX DYSTROPHY OF THE EXTREMITIES

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CHICAGO

The proper nutrition of adult tissue is the result of a balance between anabolic, or constructive, metabolic activities and catabolic, or destructive, metabolic activities. Wear and tear are replaced by repair. Injury is followed by regeneration. The forces which accomplish such an equilibrium are incompletely understood. A study of patients, therefore, in whom this balance has been disturbed is of some interest, as it may throw light on the normal control of the nutrition of tissue.

After mild trauma, usually a blunt injury affecting a wide surface or a low grade infection of traumatic or nontraumatic origin, partial injury to a nerve, frost-bite or a burn, there occurs occasionally a peculiar vasomotor and trophic disturbance which has been designated by a variety of names, depending on the outstanding symptom, such as acute atrophy of the bone,¹ traumatic angiospasm,² traumatic vasospasm,³ chronic traumatic edema,⁴ peripheral acute trophoneurosis,⁵ reflex nervous atrophy,⁵ reflex nervous dystrophy⁶ and posttraumatic osteoporosis.⁷ Obviously the authors have focused their attention on different manifestations of the same syndrome. The vasomotor disturbance, while prominent at first, may later be overshadowed by trophic changes. A hard, nonpitting edema is only one symptom and is sometimes hardly

From the Department of Surgery, University of Illinois, College of Medicine, and St. Luke's Hospital.

1. (a) Sudeck, P.: Ueber die akute entzündliche Knochenatrophie, *Arch. f. klin. Chir.* **62**:147, 1900. (b) Noble, T., and Hauser, E.: Acute Bone Atrophy, *Arch. Surg.* **12**:75 (Jan.) 1926. (c) Gurd, Fraser B.: Posttraumatic Acute Bone Atrophy, *Ann. Surg.* **99**:449, 1934; *Arch. Surg.* **32**:273 (Feb.) 1936.

2. Morton, J. J., and Scott, W. J. M.: Some Angiospastic Syndromes in Extremities, *Ann. Surg.* **94**:839, 1931.

3. Lehman, E. P.: Traumatic Vasospasm, *Arch. Surg.* **29**:92 (July) 1934.

4. (a) Klassen, P.: Ueber das chronische traumatische Handrückenödem, *Monatschr. f. Unfallh.* **36**:289, 1929. (b) Brauecker, W.: Das traumatische Oedem, *ibid.* **38**:241, 1931; (c) Pathogenese und Therapie des traumatischen Oedems, *Arch. f. orthop. u. Unfall-Chir.* **32**:577, 1933. (d) Bettmann, E., Jr.: Ueber das traumatische harte Oedem des Handrückens, *ibid.* **32**:570, 1933.

5. Zur Verth, M.: Periphere akute Trophoneurose der Hand, *Monatschr. f. Unfallh.* **30**:309, 1929.

6. Sudeck, P.: Die trophische Extremitätenstörung durch periphere (infektiöse und traumatische) Reize, *Deutsche Ztschr. f. Chir.* **234**:596, 1931.

7. Fontaine, R., and Herrmann, L.: Posttraumatic Osteoporosis, *Ann. Surg.* **97**:26, 1933.

noticeable. The osteoporosis, if systematically looked for, is often found; it should be distinguished from atrophy due to inactivity by its sudden appearance after trauma, by its spotty distribution and by the accompanying pain and vasomotor disturbance.

After the acute symptoms of a comparatively mild injury, often without damage to bones, tendons or larger vessels, have subsided, there appears a hard, nonpitting edema which is frequently accompanied by paroxysms of pain. The skin is glossy with a bluish tint, and the extremity is sensitive to draughts, to changes in temperature and to superficial and deep pressure. Sensory disturbances are indefinite; there is often a glovelike hypo-esthesia which does not follow any sensory nerve distribution. The muscles at first are hypertonic, owing to an increased reflex irritability, but later become atonic. Their electric excitability is diminished, although of normal quality. The temperature of the skin is first higher and later lower than that of the unaffected extremity; there is profuse sweating. Sometimes an increased growth of hair or a weeping eczema appears. The nails become brittle and ribbed. The bone shows a characteristic spotty atrophy, which may later become diffuse; the growing bone may be retarded in its growth, the epiphysial lines closing prematurely. The capsules of the joints shrink; movement of such joints is very painful, and mobilization of such contractures aggravates the condition. Weir Mitchell's classic description of *causalgia* closely resembles this picture.⁸

An oscillometric study of the peripheral circulation reveals first an increase and later a decrease in the height of the oscillometric curve. The minute vessels are less responsive to cold; the hyperemic reaction to cold appears much slower and lasts longer. This is an abnormal vasomotor response which in turn may result in the metabolic "trophic" disorders.

Histologic sections taken from such extremities reveal edema of the subcutis, with a shrinkage of fat, areas of minute hemorrhages and perivascular infiltrations. The latter was the outstanding feature in Lehman's cases of traumatic vasospasm.⁹ The bone in acute reflex dystrophies has been studied by Vialleton,^{8a} Fontaine and Herrmann.⁷

8. Mitchell, S. W.; Morehouse, G. R., and Keen, W. W.: *Gunshot Wounds and Other Injuries of Nerves*, Philadelphia, J. B. Lippincott Company, 1864. "Causalgic pain differs from the pain of peripheral neuritis. Outstanding feature is burning, intensified by warmth and dependent position. Stroking, manipulation, exercise accentuate it. Fright, unexpected noise, anxiety bring on a paroxysm. Hyperesthesia, wasting of tissues, atrophy of muscle and decalcification of phalanges are seen; the latter occurs when vasodilatation in the bone is present. Temperature regulation is poor; in a cool room the hand is mottled and blue; in a warm room or bath the hands feel acutely inflamed, resembling a chilblain."

8a. Vialleton, cited by Gurd.^{1c}

and Rieder⁹; they found an apposition of osteoid tissue without calcification and a spotty distribution entirely unlike any other type of atrophy of the bone.

This syndrome, if looked for, occurs not infrequently but gradually subsides; it may become, however, so intractable that a long-drawn-out disability of from 35 to 100 per cent results.¹⁰ Occasionally the arm has to be amputated, but the pain persists in the stump and radiates to the neck and shoulder. In patients in whom these symptoms and signs occur in their full intensity, a constitutional inferiority is often unmistakable. Their emotional upsets aggravate the picture.

Reflex dystrophy is often mistaken for atrophy of disuse, for artificial edema, for anxiety neurosis or for malingering. It must be differentiated from venous and lymphatic edema, from inflammatory reactions occurring around carpal and metacarpal fractures, from tuberculous or pyogenic osteomyelitis and from infection of the tendon sheaths and fascial spaces. On the lower extremity spasmodic flatfoot may simulate this condition.

The important feature of this peculiar disturbance of tissue metabolism is that an exaggeration of a nutritional reflex, which is set up by the initial injury or infection, does not subside when the effects of trauma or infection have been overcome but becomes a fixed, self-perpetuating mechanism in which the catabolic (destructive) activities are predominating. Thus the atrophy of skin, subcutis and bone may be regarded as an active process.⁶ This nutritional reflex has been described and analyzed from the physiologic standpoint by Hess.¹¹ Its adequate stimuli seem to be products of metabolism—products of digestion.

REPORT OF CASES

CASE 1.—Julia G., an 18 year old Italian girl, referred by Dr. Eric Oldberg, sustained an injury to the right wrist in an electric wringer. No fracture and no rupture of tendons or injury to large vessels occurred, but a swelling of the wrist and dorsum of the hand developed. This was treated by heat, massage and diathermy, but instead of subsiding it became definitely worse. The pain which was originally localized at the wrist, affected the fingers, which became stiff and swollen; it also traveled up to the elbow with shooting paroxysmal pain to the shoulder and the right side of the neck. The girl was highly emotional and querulous and was seeking compensation from her employer. When she was first seen, seven months after the injury, there was a hard, nonpitting edema of the dorsum of the hand extending slightly above the wrist. The fingers were stiff and were held in an extended position. The skin was glossy and moist, and the

9. Rieder, William: Das histologische Bild der akuten Knochendystrophie, *Arch. f. klin. Chir.* **177**:400, 1933.

10. Klassen,^{1a} Zur Verth.⁵

11. Hess, W. R.: Die Regulierung des Blutkreislaufes, Leipzig, Georg Thieme, 1930.

slightest draught or immersion into water of 15 C. would produce a cyanotic hue; and the patient would shriek with pain and weep. There was no evidence of injury to bones, tendons or vessels. A roentgenogram of the hand revealed diffuse atrophy, as in a late stage of traumatic osteoporosis.

The patient's mental age was 11; the intelligence quotient was 71 by the Simon-Binet test. She was rated as having a borderline mental deficiency (Miss E. Schultz). Neurologic examination by Drs. G. W. Hall and R. P. Mackay revealed no motor, sensory or reflex disturbance in the affected extremity but a definite "state of mind," an anxiety hysteria, with exaggeration of all symptoms.

Injection of 2 per cent procaine hydrochloride to the stellate and second thoracic ganglions relieved the vasomotor phenomena and stopped the pain. It was explained to the patient that first a minor operation would be performed at the wrist and should this fail to relieve the symptoms, a major operation would be performed at the neck. Accordingly, the median nerve and the ulnar and radial arteries were stripped of their sheaths. The median nerve was surrounded by a fine layer of hyperemic connective tissue. After operation the pain subsided, and physical therapy could be started without causing pain. All symptoms except the pain in the shoulder and in the cervical region disappeared. The patient's state of mind improved. Three months after the operation she admitted that she had regained the use of her hand. The pain along the brachial plexus had improved. She was again encouraged and told that a further operation, namely, cervicothoracic ganglionectomy, would relieve the pain if that seemed to persist. Six months after the operation she reported complete recovery.

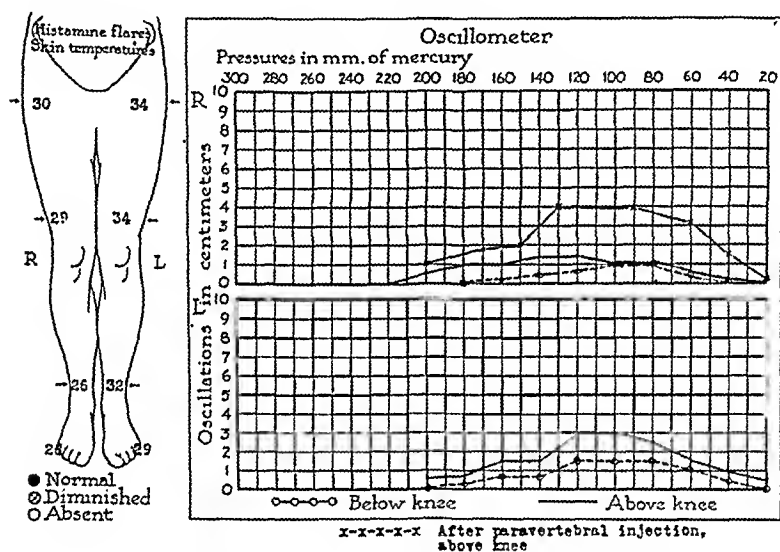
The important factors operating in this case were: (1) a constitutional inferiority manifested by the patient's low mental age and low intelligence quotient; (2) an unsuitable environment, the patient being urged by her mother and a lawyer to obtain maximal benefits from the injury, and (3) a definite reflex dystrophy, originating at the site of injury around the median nerve, which could be interrupted by removal of the irritating focus and a partial periarterial sympathectomy. The condition in this case could readily be called *causalgia*.

CASE 2.—J. H., a 41 year old unmarried woman, had received radium therapy and had undergone dilation and curettage at the Mayo Clinic in 1932 for menorrhagia. Six months later hysterectomy and ovariectomy on the right side were done in Cleveland for multiple fibroid tumors. Both after the insertion of radium and after the hysterectomy there occurred an attack of pain in the right groin, with a swelling of the thigh, which was diagnosed as thrombosis of the external iliac vein. The patient stayed in bed for four months with considerable pain. There was no elevation of temperature. On her admission to St. Luke's Hospital on Aug. 4, 1935, there were no abnormal findings except those referable to the right lower extremity. There were unilateral vasospasm extending from the toes to the groin, a peculiar paresthesia of the stocking type which did not follow any peripheral nerve and sensitivity to heat and cold. The patient hesitated to put weight on the limb and walked on crutches. The limb was atrophic, there being a difference of 1 inch (2.5 cm.) in circumference 6 inches (15.3 cm.) below the knee. The skin was scaly, and the muscles were flaccid. Neurologic examination by Dr. R. P. Mackay revealed nothing abnormal in the central nervous system and an "old maid" personality, but not enough to cause any trouble. The patient had a definite mother and brother fixation and stated that she had no heterosexual feelings. The pain was not considered hysterical.

A paravertebral injection of procaine hydrochloride into the second, third and fourth lumbar segments resulted in a complete sympathetic paralysis of the right lower extremity. It abolished the difference in temperature and produced a dry skin. All movements, including hyperextension of the knee and thigh, were free and painless (fig. 1).

Roentgen examination revealed spina bifida occulta at the top of the sacrum. To rule out the possibility of a urinary obstruction causing the pain, an intra-

Name	J. H.		Date	8-6-35	
Pulse	Right	Left	Pulse	Right	Left
Femoral.....	1 (3)	3	Axillary.....		
Popliteal.....	1 (3)	3	Cubital.....		
Post. tibial.....	2 (3)	3	Radial.....		
Dorsalis pedis.....	2 (3)	3	Ulnar.....		
Blood pressure.....			Blood count.....		



Room temperature: 72 F.

Toe temperature:

lumbar sympathetic

Before peripheral nerve block

26

After peripheral nerve block

33

Summary of findings: A diminution of arterial inflow into the right lower extremity is shown by lower skin temperatures, and lower and flatter oscillometric curves. That this is not of organic origin is shown by the findings following paravertebral injection when the difference between the two sides was abolished.

Fig. 1.—Circulatory record of J. H. After paravertebral injection the difference in pulse rate, skin temperature and oscillometric curves was abolished, indicating a central or reflectoric sympathetic stimulation.

venous pyelogram was made, with completely negative results. The basal metabolic rate was minus 2 per cent. The sedimentation rate was within normal limits, indicating the absence of even a latent phlebitis. The blood count was normal. On August 26 the right iliac vessels were explored through an anterolateral extra-peritoneal incision. Dense fibrous tissue was found around the external iliac vessels, chiefly encasing the vein. The vessels were completely stripped of this tissue, which contained enlarged lymph glands.

The convalescence was uneventful. The histologic study of the removed tissue revealed small lymph nodes with a moderate hyperplasia of the mononuclear cells and fibrous tissue around the glands (Dr. E. F. Hirsch).

The patient was reexamined two weeks, four weeks and three months after operation. The pain, paresthesia and sensitivity to cold disappeared. She had used the leg freely without crutches and rode horseback ten weeks after the operation with no return of symptoms. The leg increased in size, there being only a $\frac{1}{4}$ inch (0.6 cm.) difference in the circumference of the calf 6 inches below the knee. There was no cyanosis in the dependent position and no pain on walking. The oscillometric curves and skin temperatures were identical for the two limbs. Five months after the operation the patient reported complete recovery.

The case was interpreted as one of reflex dystrophy originating from a pelvic lymphangitis and periphlebitis, which in turn was activated by the insertion of radium. After the vein was stripped, the focus of irritation was disconnected from the cord.

CASE 3.—Mrs. D. R. J., 25 years old, referred by Dr. Charles A. Elliott, was first seen on Sept. 2, 1935. Three years previously, after the normal delivery of a healthy boy, there gradually developed a painful cyanosis of the lower extremities. The skin became mottled. Paroxysms of pain would occur after exposure to cold or heat or even on standing. The skin became scaly and slightly atrophic. The feet were always cold. Repeated examinations by Dr. Hillis revealed normal pelvic organs. A pelvic thrombosis was suspected but could not be substantiated. Studies of the blood, including the platelet count, coagulation time, bleeding time and blood calcium determination, revealed normal figures. The basal metabolic rate was normal.

On physical examination the peculiar mottling of the skin was very definite. At certain places these cutaneous venules seemed thickened and nodular. During an examination at the Billings Hospital, Dr. Paul Bucy performed a biopsy of such a nodular vein and sent me the specimen for study. The histologic section of this vein revealed a cushion of intimal and subintimal tissue, the remnants of an old nodular phlebitis (Dr. Sol Rosenthal, University of Illinois).

A block of the second, third and fourth sympathetic ganglions with procaine hydrochloride temporarily abolished the coldness, perspiration and mottling. The limbs felt normal, without any evidence of other than sympathetic paralysis. Lumbar sympathectomy was advised, but has not been carried out so far.

In this instance the reflex dystrophy probably originated after childbirth from the nodular phlebitis, which may have had an infectious or a metabolic basis. The condition has been stationary for three years, and sympathectomy seems justifiable.

CASE 4.—Mr. H. S., a 25 year old, well built, muscular man, was grinding the spark plugs of his car, when he was suddenly seized with pain in the right axilla, shooting into the right arm. The arm promptly began to swell. He went to bed and elevated the arm. The acute pain subsided, but there remained a permanent swelling of the arm and a deep boring pain after muscular exercise, accompanied with a widespread arterial flush. When he was seen eight months after the injury, the diagnosis of axillary thrombosis caused by effort was made. Outside of an obvious venous obstruction characterized by development of collateral channels over the chest (fig. 2), a lower oxygen content of the cubital vein on

the affected side and a block of the subclavian vein under the pectoral muscle visualized by an intravenous injection of skiodan (fig. 3), the patient presented a peculiar vasomotor instability of the affected arm. On muscular effort a wide-spread flare was visible. The oscillometric curves were higher on the affected side. There was a persistent edema, which was only slightly influenced by posture. On June 8, 1933, the subclavian vein was exposed on the anterior wall of the chest, below the pectoral muscles. It was found to be a fibrosed cord, surrounded by considerable perivenous adhesions. The artery was completely free and pulsated well. The vein was stripped from its adhesions for a distance of 4 cm. (1¾ inches). The vein was not resected, as a future recanalization was still thought to be possible. Immediately after the operation, the pain on exercise, the vasomotor instability and the edema subsided; although the venous obstruction had not been relieved. The patient has had no recurrence of symptoms for two and one-half years and does heavy work.



Fig. 2—Infra-red photograph of the anterior wall of the chest. There is a marked increase of the venous collateral network on the affected (right) side.

This case was interpreted as one of traumatic axillary thrombosis which set up a vasomotor reflex, which was responsible for the flushing and the pain and even for part of the edema. Since the edema disappeared after the afferent arc of the reflex was interrupted, it was not due, or not entirely due, to the venous obstruction.

CASE 5.—B. H. a 38 year old laborer, was first seen in the neurocirculatory disease clinic of the University of Illinois College of Medicine on Nov. 19, 1935, complaining of pain and stiffness of the left foot and ankle. He was quite well until last June, at which time he opened a small abscess below the left external malleolus. In a few days the foot became swollen and painful, and the patient had to stay in bed with a severe infection. The original opening drained little, but the swelling involved the whole foot and ankle. In July a cast was put on, but the leg became so painful that the patient cut the cast off in forty-eight hours. Another loose cast was applied and left on for a week or ten days. Since then the patient has been up and around, limping and hobbling on crutches. The ankle was stiff, and weight bearing was painful.

The physical examination revealed nothing of note, with the exception of the affected extremity and chronic bronchitis. The left lower extremity was definitely atrophic compared with the right (fig. 4). The measurements of the thighs and calves revealed a difference of $1\frac{1}{2}$ inches (3.8 cm.) in circumference of the thigh and $1\frac{1}{4}$ inches (3.2 cm.) at the midcalf.

The musculature of the calf was definitely shrunken compared with the normal side but seemed in a state of hypertonus. The skin was cold, and there was a cyanotic discoloration of the entire foot, especially in the depending position. The pulsations of the arteries seemed normal. The motion in the ankle joint was limited to 5 degrees. There was a marked valgus position of the ankle.



Fig. 3.—Visualization of the axillary and subclavian veins by the injection of skiodan into the cubital vein. The block in the subpectoral portion of the subclavian vein has been accentuated by retouching the print. It was very definite in the film. There is a marked filling of the cephalic vein which serves as the main collateral. This was absent on the left side, used for control. The subpectoral portion of the subclavian vein is quite distinct.

Below the outer malleolus a small pigmented scar was seen, which was freely movable and not attached to the bone. This was the site of the original infection. Pain was felt on dorsiflexion and on putting weight on the leg. Cutaneous sensation and the reflexes were normal. Paresthesia involving the whole foot was present. There was no element of compensation in this case.

Oscillometric curves taken before the operation revealed an increased inflow of blood into the lower extremities; in the left leg oscillations started at 280 mm. of mercury, and the diastolic pressure was read at 105 mm.; on the normal leg the oscillations were seen even at 300 mm., and the diastolic pressure was read at 75 mm. The lower systolic pressure here could readily be explained by the smaller size of the limb, whereas the definitely higher peripheral resistance might have been due to increased spasm or an organic obstruction. As the pedal pulses were well palpable, the latter possibility is not likely.

After the administration of 100 mg. of procaine hydrochloride intraspinally, resulting in anesthesia to the level of the navel, the blood pressure in the left lower extremity fell to 140 systolic and 85 diastolic and in the right lower extremity to 140 systolic and 80 diastolic, making them practically equal. This fall in pressure and the striking diminution of the stroke volume were not accom-



Fig. 4.—Marked atrophy of the left leg and thigh following a low grade chronic infection of the subcutaneous tissue at the external malleolus. The picture has been reversed.

panied by a fall in blood pressure in the arm, which stayed at 115 systolic and 75 diastolic during the entire period of anesthesia. A week after left lumbar sympathectomy was performed the pulse waves of the lower extremities seemed fairly identical; the left was 160 systolic and 81 diastolic, and the right, 155 systolic and 85 diastolic, with slightly higher waves on the right side. This is readily explained by the difference in the size of the limb.

Roentgen examination of the ankles and the lower part of the legs revealed marked atrophy of the spongiosa and cortical shells of the tarsal and metatarsal bones, of the calcaneus and the femur, of the tibia and the fibula (fig. 6).

The patient was followed in the dispensary after the operation. Four weeks later he was stepping on the affected leg quite freely. He still had a partial

ankylosis of the ankle, which because of lack of adequate physical therapy had not had active and passive exercise. He was instructed to apply heat and to massage the ankle at home.

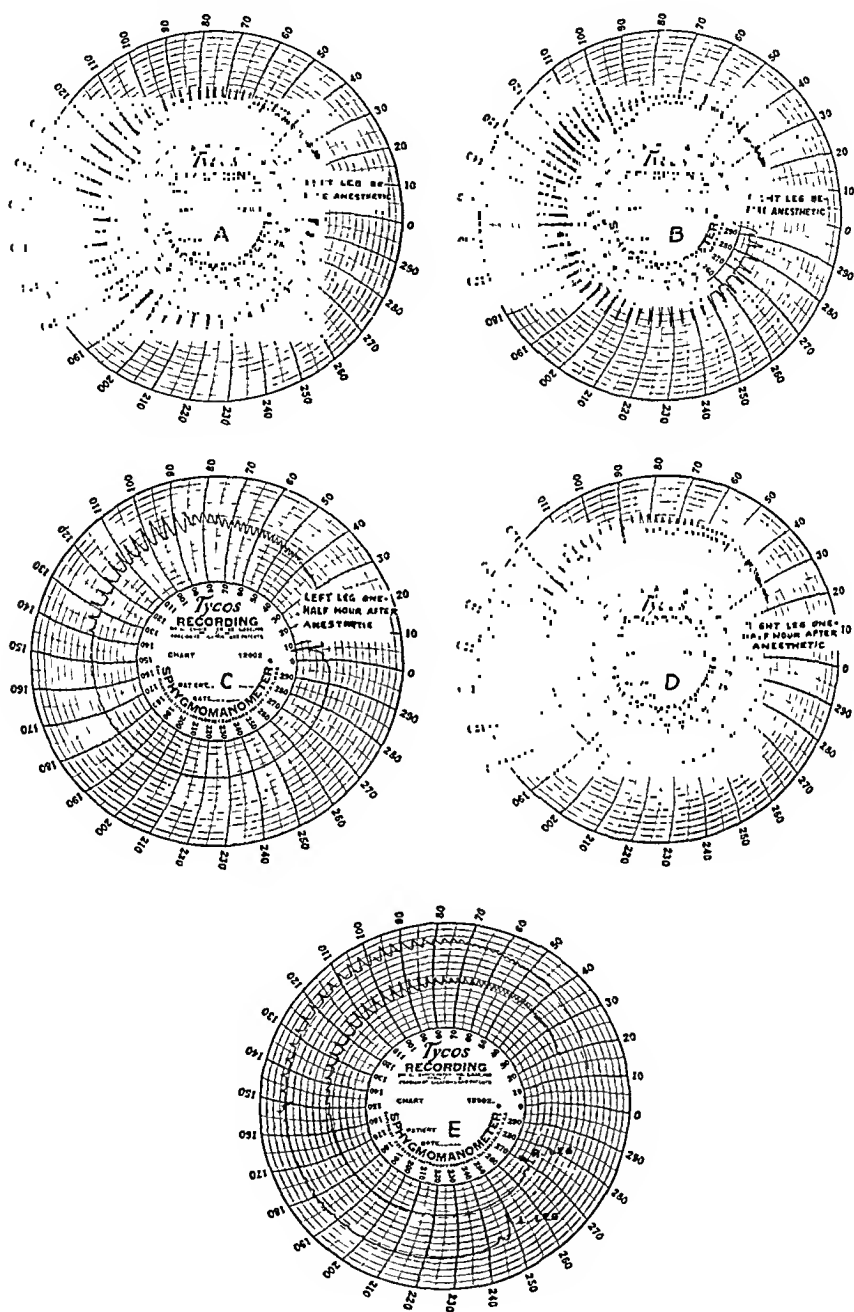


Fig. 5.—Oscillographic curves in case 5 illustrating the marked increase in inflow into the lower extremities (A and B) which was abolished after spinal anesthesia (C and D) and after lumbar sympathectomy (E). In E the lower curve was made from the affected left leg after lumbar sympathectomy and the upper curve from the normal extremity.

Six weeks after the operation walking was painless. The crutch was abandoned. There was still a limitation in dorsiflexion, but plantar flexion was free. The patient had not used the leg much because of the unusually heavy snowfall. Three months after the operation the saturation of venous oxygen, which rose immediately after sympathectomy, was maintained. The vasomotor disturbances had disappeared. The ankylotic ankle joint and the valgus position of the ankle still caused trouble. Because of external circumstances, the patient was unable to obtain any kind of physical therapy, but a few active and passive exercises were prescribed, together with an adequate arch support.

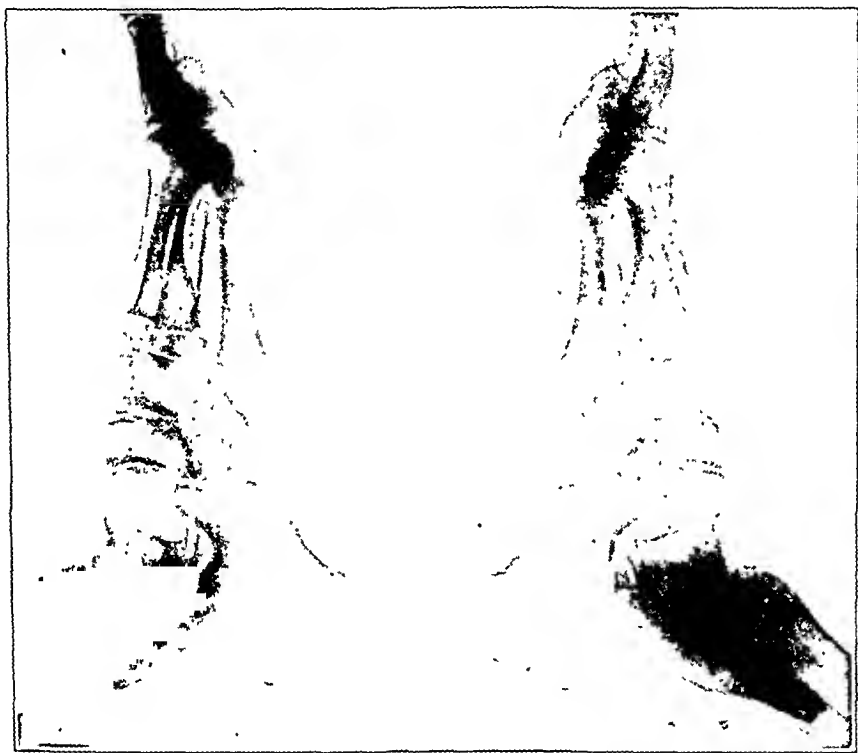


Fig. 6.—Atrophy of the spongiosa and cortical shells of the calcaneus and the tarsal and metatarsal bones. The control film is on the left.

COMMENT

In the five cases presented the initial stimulus for the vasomotor and trophic changes included a single mild trauma (case 1), massive venous thrombosis (case 4), pelvic periphlebitis (case 2), nodular phlebitis (case 3) and a neglected infection (case 5). The common factor in all these cases was the rather mild and insignificant injury to the tissue which caused the widespread trophic disturbance in the affected limb. It is obvious that a large number of such injuries, infections or thromboses occur day after day without producing such consequences. Why, then, one must ask, will this syndrome appear in certain, seemingly rare cases?

To answer this question one must first inquire how rare or how frequent this "reflex dystrophy" really is. Since my attention has been focused on this syndrome, I have found it in a great many cases of venous thrombosis, blunt trauma, lymphatic block or low grade infection. These vasomotor and trophic changes, however, are slight and gradually subside. I have also repeatedly seen a marked hard edema accompanying Buerger's disease disappear immediately after sympathectomy, thus demonstrating that it is not always due to venous block. One must say then that although in its full, intractable form the disease is infrequent, mild, masked abortive forms can frequently be observed, but they will spontaneously subside with the healing of the original exciting cause.

What is it that makes this peculiar disease so intractable that a number of patients requested and were granted amputation? In my small series the patient in case 1 definitely had borderline mental deficiency, with a low intelligence quotient; there was also the element of compensation in this case. In all my other patients, with the exception of the one in case 4, a physically and mentally normal, husky young man, an imbalance of the vegetative nervous system and a neurotic constitution could easily be detected. A neurotic constitution is obviously not easily defined and is so often referred to as constitutional inferiority. It is interesting to note, however, that the spinal mechanism, whereby the preganglionic neurons of the sympathetic nervous system can be activated by somatic nociceptive stimuli, is not as active if the medulla and the higher centers retain their normal connections with the spinal sympathetic outflow. The application of the work of Brooks¹² to this problem means that if the inhibition of higher centers is lacking or diminished, this spinal somatic-sympathetic reflex may become exaggerated or fixed.

Acute reflexes, especially those originating from diseased or thrombosed veins and arteries, are well known, and I have recently commented on the important reflex vasospasm which accompanies sudden arterial occlusions and which may often—and not the original plug itself—be the cause of gangrene.¹³ As long as the peripheral blood vessels lack any other but somatic afferent nerves,¹⁴ the afferent arc must follow the ordinary sensory pathways and enter the posterior horn through the posterior root ganglion. Because lumbar sympathectomy

12. Brooks, C. M.: Reflex Activation of the Sympathetic Nervous System in the Spinal Cat, *Am. J. Physiol.* **106**:251, 1935.

13. de Takáts, G.: Acute Arterial Occlusions of the Extremities, *Am. J. Surg.* **33**:60, 1936.

14. Moore, R. M., and Singleton, A. O., Jr.: Studies on the Pain Sensitivity of Arteries: II. Peripheral Paths of Afferent Neurons from the Arteries of the Extremities and of the Abdominal Viscera, *Am. J. Physiol.* **104**:267, 1933.

abolishes the danger of gangrene from high arterial ligation,¹⁵ the efferent arc of this reflex must go through the sympathetic efferent nerves which leave the cord from the lateral horn through the anterior roots, join the peripheral mixed nerves and are given off to the vessels in segments. Such an acute reflex vasospasm may last—if untreated—for from twenty-four to forty-eight hours and is due to a sudden powerful stimulation of sensory nerves, especially—it would seem—around blood vessels.

In these cases of reflex dystrophy, however, a slow, continuous afferent impulse is being dealt with which may have vasoconstrictor (pressor) or vasodilator (depressor) effects. It is a long known fact of physiology that strong stimulation of the central end of an afferent nerve elicits pressor effects, whereas weak stimuli or stronger stimuli in a regenerating nerve produce depressor effects. The local depressor effects of stimulation of sensory nerves have been described by Lovén and are usually named after him. These effects have been studied by Bayliss¹⁶ (fig. 7). Lovén found that stimulation of the divided central end of a sensory nerve in the rabbit's ear caused marked vasodilatation in the ear, which in turn could be prevented by cutting the cervical portion of the sympathetic trunk. He also found that when a peripheral nerve in the hindleg was stimulated, the volume of the limb increased. Bayliss felt that dilatation of the vessels causing the increase in the size of the limb was due both to excitation of dilator fibers and to inhibition of constrictor fibers. He assumed that all dilator fibers were in the posterior root and that the abdominal sympathetic nerves carried only constrictor fibers (fig. 8), a thesis which has received modification since his time.¹⁷

The difference in the vasomotor responses elicited by weak and strong stimulation of afferent nerves can be explained, according to Ranson and Billingsley,¹⁸ by the variations in the resistance to afferent conduction offered by different central pathways. According to their findings, weak impulses reaching the spinal cord are conveyed upward in the depressor path, in the ventral parts of the lateral funiculi containing long fibers with few relays, whereas the pressor impulses are con-

15. Mulvihill, D. H., and Harvey, S. L.: Studies on Collateral Circulation: Thermal Changes After Arterial Ligation and Ganglionectomy, *J. Clin. Investigation* 10:423, 1931.

16. Bayliss, W. M.: *The Vasomotor System*, London, Longmans, Green & Company, 1923.

17. Lewis, Thomas, and Pickering, G. W.: Vasodilation in the Limbs in Response to Warming the Body, with Evidence for Sympathetic Vasodilator Nerves in Man, *Heart* 16:33, 1931.

18. Ranson, S. W., and Billingsley, P. R.: Vasomotor Reactions from Stimulation of the Floor of the Fourth Ventricle, *Am. J. Physiol.* 41:85, 1916.

ducted upward at the apexes of the dorsal gray columns through paths composed of short fibers with frequent relays.

To apply these studies to the present problem, the possibility of different reflex paths must be considered. Andrews published the report of an interesting case of edema following radical amputation of the breast in which section of the posterior roots was done for the intractable pain.¹⁹ The edema promptly disappeared and only reoccurred after a week. In his diagram the vasomotor reflex arc is led through the sympathetic chain to the posterior root ganglion and from there into the posterior horn; the efferent arc is through the anterior roots, joining the vessels through the sympathetic nerves. Since the findings of Moore and Singleton,¹⁴ who could elicit a painful response from a peripheral vessel after lumbar sympathectomy, it seemed likely that sensation from the arteries of the extremities is mediated by the spinal nerves. And

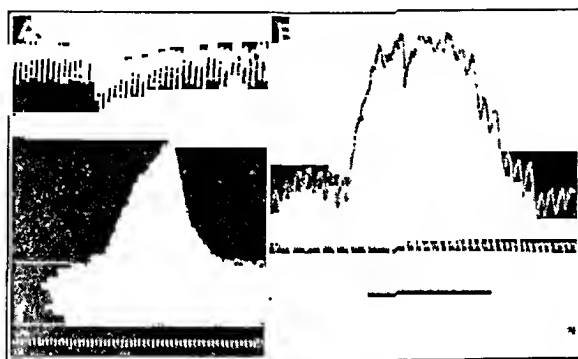


Fig. 7.—Curves showing the Lovén reflexes. In *A*, the upper curve represents the blood pressure; the lower curve, the volume of the upper part of the hindlimb of a dog. At the mark of signal the central end of the dorsalis pedis nerve of the same leg was stimulated, causing marked dilatation of the leg with a slight fall in blood pressure. The usual rise of general pressure was absent here. In *B*, the upper curve represents the blood pressure; the lower curve, drops of blood falling from the cut femoral vein. At the mark of signal the central end of the anterior crural nerve was stimulated. A rise of blood pressure is seen, accompanied by vasodilatation in the leg. (From Bayliss, W. M.: *The Vasomotor System*, Longmans, Green & Company, London, 1923.)

yet the fact remains that certain painful syndromes in the extremities, such as causalgia, stump neuralgia and meralgia paraesthetica, are favorably influenced by blocking the sympathetic nervous system with procaine hydrochloride or by sympathectomy. In accordance with a diagram which I published to explain the acute reflex vasospasm following arterial occlusion, sympathectomy may act by interrupting the efferent arc, thus abolishing the reflex vasomotor, pilomotor and sweat-

19. Andrews, E.: *The Vasomotor Reflex Arc*, *Ann. Surg.* 85:116 (Jan.) 1927.

ing phenomena (fig. 9). In cases 2, 3 and 5 there was evidence that such a reflex was successfully interrupted by sympathectomy. In cases 1 and 4, however, the focus of irritation on the afferent side was eliminated, resulting in equally good results. One cannot discuss, however, such nutritional reflexes without considering the vasodilator fibers in the posterior roots. Some evidence has recently been accumulating that there are vasodilator efferent fibers in the dorsal roots with cells of origin in the dorsal root ganglions, accessible to reflex activation via synapses within the cord.²⁰ The literature on the production of vasodilatation by stimulation of the posterior roots has been summarized by Kahr and Sheehan.²¹ But so long as such fibers can be sectioned only by sacri-

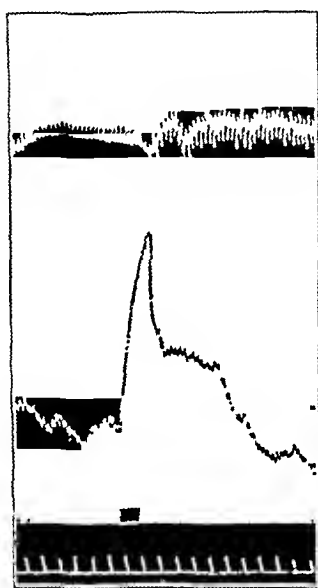


Fig. 8.—Excitation of posterior root vasodilators in the Lovén reflex. The upper curve indicates the blood pressure; the lower curve, the volume of the hindlimb of a dog. The abdominal sympathetic nerves were extirpated and the viscera removed. At the mark of signal, the central end of the anterior crural nerve of same leg was stimulated. (From Bayliss, W. M.: *J. Physiol.* 28:276, 1902.)

ficing the sensation of the extremity, their interruption is not practicable except in cases of intractable pain. When disease destroys the posterior roots, as in tabes, syringomyelia and spina bifida, trophic ulceration occurs. Treatment by sympathectomy has been entirely unsuccessful in my hands. The reasons for this are the absence of axon reflexes and

20. Bishop, G. H.; Heinbecker, P., and O'Leary, J. C.: The Function of the Nonmyelinated Fibers of the Dorsal Roots, *Am. J. Physiol.* 106:647, 1933.

21. Kahr, S., and Sheehan, D.: The Presence of Efferent Fibers in Dorsal Roots, *Brain* 56:205, 1933.

possibly the lack of any spinal reflexes activated by somatic impulses.

The oscillometric studies in case 5 have revealed the interesting fact that in the affected dystrophic extremity as in its fellow a continuous depressor reflex (Lovén reflex) was operating which was equally abolished by spinal anesthesia (afferent arc) and by lumbar sympathectomy (efferent arc). The spinal anesthesia might, of course, have affected the sympathetic efferent nerves, although it did not reach high enough to abolish sweating above the knee. In case 2 there was definite vasoconstriction, which occurs, according to Sudeck^{1a} and Fontaine and Herrmann,⁷ in the later stages.

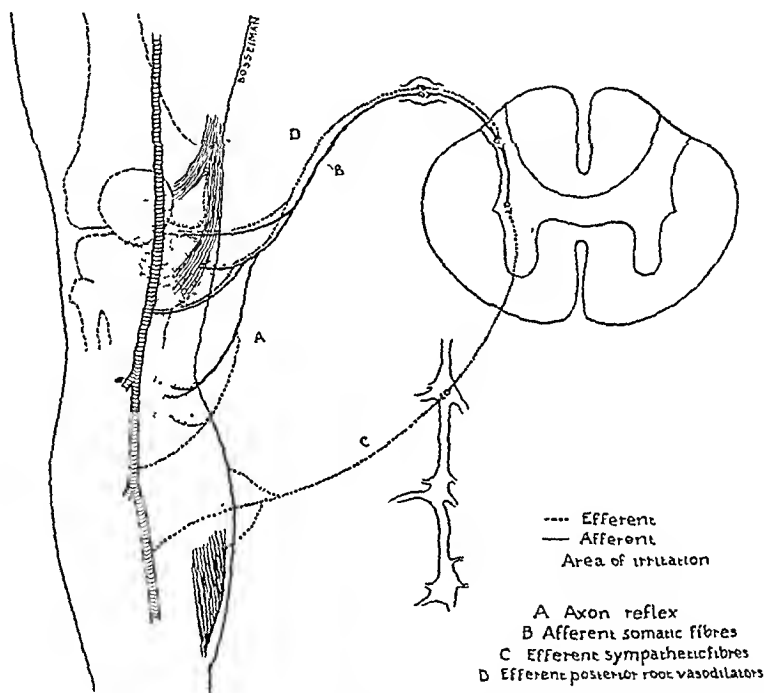


Fig. 9.—Vasomotor and nutritional reflexes originating in the tissues. Clinical experience would indicate that such stimuli are especially apt to originate around blood vessels and joints and tendons.

Gask and Ross²² gave a different explanation for the beneficial effect of sympathectomy in a case of causalgia associated with herpetic vesicles. They expressed the belief that the increased flow of blood after sympathectomy insures the rapid removal of tissue products, including the H substance which dilates vessels and forms herpetic vesicles. Following the work of Sir Thomas Lewis, they explained the vasomotor phenomena of causalgia on the basis of an antidromic impulse originating from an irritated sensory nerve. While this mecha-

22. Gask, G. E., and Ross, J. P.: *The Surgery of the Sympathetic Nervous System*, Baltimore, William Wood & Company, 1934.

nism may be operating in certain types of causalgia, my cases show that small foci of irritation may maintain a widespread vasomotor and trophic disturbance which can be relieved by interrupting either the afferent or the efferent arc of the reflex. While many authors, starting with Sudeck, have spoken of a reflex trophoneurosis, the pathway of such a reflex has not been examined in detail.

CONCLUSIONS

The most likely pathway, then, for this peculiar nutritional reflex, which must be differentiated from the short axon reflexes or from vasodilator responses to stimulation of the efferent nerves in partial injury to the nerves, is a chronic focus of irritation in the periphery, a weak, continuous impulse through ordinary sensory pathways to the cord and a relay, following the pathway of least resistance to the lateral horn, and from here a sympathetic efferent impulse to the tissues. That this reflex is more active when higher centers are not inhibited has been shown experimentally, and this may explain why reflex dystrophy occurs more readily in mentally unstable or defective persons. It is obviously not easy to differentiate it in its early forms from malingering, anxiety neurosis or hysteria. A temporary block of the sympathetic outflow is of great diagnostic aid. The spotty atrophy of the bone, which occurs very early, is another important sign. At a later stage the atrophy of the skin, nails and muscles becomes evident; the atrophy of the bone is now diffuse and cannot be differentiated from atrophy due to inactivity. That low grade infection in the bones, joints and tendons should be carefully excluded is obvious.

The excision of the irritable focus was possible in three of my cases; should this be impossible, the efferent arc of the reflex can be interrupted by sympathectomy, which seemed equally effective. This operation has been recently advocated by Brauecker²⁰ and Rieder²² for such conditions. Reflex dystrophy has been unrecognized for many years and should be particularly understood by men engaged in estimating disability after injuries. It occurs frequently but usually subsides under mild, not overzealous physical therapy. Heat, immobilization and diathermy have been successful in many of the cases of milder involvement; the patients for whom I advised sympathectomy had already been found resistant to conservative therapy before the afferent or efferent arc of the reflex was interrupted. These cases also show that outside of fractures, injuries and infections of the soft tissues, venous thromboses and periphlebitis are also capable of activating this reflex.

23. Rieder, W.: Operative Behandlung der akuten schweren Extremitätendystrophie, *Arch f klin Chir.* 180:368, 1934

SUMMARY

Five cases of reflex dystrophy of the extremities have been described. One followed a mild injury to the soft tissue, one a pelvic lymphangitis, one an axillary thrombosis, one a nodular phlebitis of the veins and one a low grade infection of the soft tissues. In all of these cases the local alteration of tissues maintained an exaggerated nutritional reflex, leading to vasomotor and trophic phenomena. The possible pathways of this reflex were discussed, together with methods of treatment.

NOTE.—Since this article was submitted for publication, four additional cases have been observed; in one the condition followed a mild injury to the foot; in one, lymphangitis of the toe; in one, an injury to the wrist by strapping on the operating table, and in one, an injury to the middle finger. In the last case, in addition to an increased blood flow, there were marked herpetiform eruptions. In two of the cases sympathectomy had been performed, with cessation of symptoms. All four cases support the observations made in the article.

SIXTY-SECOND REPORT OF PROGRESS IN ORTHOPEDIC SURGERY

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CONGENITAL DEFORMITIES

Congenital Dislocation of the Hip.—Bauer¹ condemns the treatment of congenital dislocation of the hip by a plaster cast, maintaining that there is no growth in the joints during such fixation. Even if immediately after such treatment the function seems good, arthritis or subluxation occurs later. He is of the opinion that early recognition of the condition can be made, i. e., in the fourth to the eighth week, by observing the posture of the infant. At this age replacement is secured without an anesthetic, and the position is maintained by the application of a webbing brace so arranged that the knees are drawn apart by attaching them to a band around the lower part of the thorax. Natural mobility is unhindered, only adduction and extension of the hip being prevented, and very good musculature develops, especially around the hip. The result of the treatment in all cases is a rapid mechanical cure without danger of recurrence, owing to the natural development of the joint and its soft parts. Twenty-seven children have been treated by

This report of progress is compiled from a review of 148 papers selected from 306 titles relating to orthopedic surgery, which appeared in the medical literature approximately between July 1, 1936, and Nov. 1, 1936. Only those which suggested progress were chosen for review.

1. Bauer, F. Congenital Dislocation of Hip, *Lancet* 1:1057-1059, 1936.

this method, 21 of whom were in the first year of life and the remaining 6 of whom were in the second year.

The Acetabular Index in Infants in Relation to Congenital Dislocation of the Hip.—In a study of normal and of congenitally dislocated hips Kleinberg and Lieberman² draw attention to the angle of inclination of the roof of the acetabulum as an index of dislocation or subluxation. They coin the term acetabular index and define it as the angle formed between the roof or iliac portion of the acetabulum and a horizontal line passing through the triradiate cartilages. They found this index to average 27.5 degrees in normal infants. In infants of 2 years the normal angle averaged 20 degrees. In those with congenital dislocation of the hip the average index was 37.5 degrees. If the index is 30 degrees or more in an infant, they suggest that the hip is in danger of slipping out and should be treated in abduction, as advocated by Putti.

[ED. NOTE.—Efficacy in the treatment of congenital dislocation of the hip seems to depend chiefly on early diagnosis and early fixation with the thighs in abduction. Later therapy must usually consist of extensive operative procedures, with no definite assurance of success.]

Treatment of Pes Adductus.—Dengler³ discusses the treatment of pes adductus from a review of 32 cases. Two thirds of the patients were males, and in 23 the deformity was bilateral. There were metatarsus varus and deformity of the tarsal bones on the medial side of the foot in most cases. In 17 patients (young patients with mild deformity) manual manipulation and the use of plaster casts sufficed. In 2 cases it was necessary to perform manipulation under anesthesia. Seven patients were operated on after the manner of Camera, the fascia and joint capsule at the scaphoid-cuneiform and first metatarsal joints being stripped. In the remaining 6 cases (older patients, from 5 to 11 years), a wedge-shaped osteotomy of the cuboid bone was necessary in addition to the operation of Camera.

Congenital Flexion and Ulnar Deviation of the Fingers (Deviation in Coup de Vent).—Dreyfuss⁴ reports 4 cases of congenital deformity of the fingers in flexion and ulnar deviation. He believes that the chief factor in their causation was a contraction in the volar accessory ligament. In no case was any bony abnormality observed. Other associated

2. Kleinberg, S., and Lieberman, H. S.: The Acetabular Index in Infants in Relation to Congenital Dislocation of the Hip, *Arch. Surg.* **32**:1049-1054 (June) 1936.

3. Dengler: Zur Klinik Therapie der Pedes adducti, *Ztschr. f. Orthop.* **65**: 121-129, 1936.

4. Dreyfuss, M.: Beitrag zum Bilde der angeborenen "Windmühlenflügelstellung" der Finger (*Déviations des doigts en coup de vent*), *Ztschr. f. Orthop.* **65**:205-225, 1936.

deformities, such as clubfoot, were not uncommon. Operative correction was attempted in 2 cases. A tourniquet was used; an incision was made between the fingers, and the joint capsule and aponeurosis were incised on the lateral side of the finger. The accessory volar ligament was freed at its distal end. The superficial fibers of the adductor pollicis and opponens pollicis muscles were cut, permitting the thumb to be brought into abduction. The hand was placed on a splint in the corrected position. The author reports almost complete correction of the deformity and good function after operation.

[ED. NOTE.—One of the editors has observed marked improvement in 2 cases after daily passive stretching with a corrective hand cast worn at night.]

Scoliosis in Infants.—Harrenstein⁵ reports 46 cases of scoliosis in infants under 2 years of age. None of these showed any congenital abnormalities. All had rotation deformity of the ribs, and none had rickets. The girls outnumbered the boys 29 to 17. In 37 of the 46 infants a single curve was present, it being to the left in 29; in the remaining 9 double scoliosis was present. The cause of these curves was unknown. Treatment consisted of complete recumbency in corrective plaster shells. The treatment was kept up for as long as two years if necessary. When the patient was first allowed up, a supporting corset was worn. In 50 per cent of the cases the condition was considered cured at the end of a follow-up period of from one to six years.

SYPHILIS

Congenital Syphilis of the Bone.—By a study of roentgenograms, Jung⁶ was able to diagnose congenital syphilis when the serologic test was negative. He quotes the figures given by McLenvey and Turner. Of 54 infants born of syphilitic mothers, with a positive Wassermann reaction of the cord blood, 81.4 per cent were ultimately found to be syphilitic. Of 283 infants also born of syphilitic mothers but with a negative Wassermann reaction of the cord blood, only 13.7 per cent were found to have congenital syphilis. It may be said that negative roentgenographic findings are not conclusive, but that positive roentgenographic findings offer one of the most conclusive and one of the earliest diagnostic signs of congenital syphilis. Jung analyzes the roentgenographic findings in 62 cases of syphilis in infants under 1 year of age. He discusses osteochondritis, which is described as an increase in the width of the provisional zone of calcification of the long bones, which is shown roentgenographically as a dense cap at the diaphysial end.

5. Harrenstein, R. J.: Sur la scoliose des nourrissons et des jeunes enfants, Rev. d'orthop. 23:289-307, 1936.

6. Jung, T. S.: Congenital Bone Syphilis, Chinese M J 50:352-363, 1936

When this lesion is farther advanced it should be considered as an osteomyelitic change. Actual osseous destruction may be seen, and there may occur an infraction of the zone of provisional calcification. Osteomyelitis is the most common lesion in advanced osteochondritis and is most frequently characterized by punched-out symmetrical rarefactions which are seen in the upper and inner aspects of the tibia. Periostitis is discussed in detail. It is seldom found as the sole lesion of congenital syphilis in early infancy but usually accompanies advanced osteochondritis. Excellent roentgenograms are shown.

OSTEOMYELITIS

Dengler⁷ reports 38 cases of osteomyelitis. In 23 of these cases the patients were treated by Orr's method of drainage, petrolatum packs and undisturbed rest in a cast. The remaining 15 were treated by Löhr's modification (extreme drainage, resection into normal bone, cod liver oil packs, interrupted suture of the skin, the application of a cast and rest). In 23 of the 38 cases the lesions completely healed. At the time of the report it was more than nine months since operation in all the cases. The details are not given. Eight of the patients had tiny fistulas, and in 7 small sequestrums had been picked out. Both methods of treatment seemed about equally effective.

Pusitz and his co-workers⁸ review the literature on osteomyelitis of the spine and report 6 additional cases. They point out numerous errors that are commonly made in diagnosis. Certain general principles in therapy are given: Drainage of the osteomyelitis should usually be delayed until the diagnosis and the area involved are known. The patient should be kept on a Bradford frame with head and pelvic traction if there is much pain on motion. Transfusion of blood is the most effective supportive measure. The Orr treatment for vertebral lesions is advocated. Fusion of the involved area of the spine may be necessary later. Dependent drainage of abscesses should be carried out when possible. Where there are signs of compression of the spinal cord, laminectomy usually brings prompt relief.

Disturbance of Growth Following Osteomyelitis.—Wilson and McKeever⁹ studied 57 patients with 85 individual foci of osteomyelitis. Sixty-two per cent of the bones showed some sort of a disturbance of growth on clinical examination. Hypertrophy of the diameter of the

7. Dengler: Zur Behandlung der chronischen Osteomyelitis nach Orr und Löhr, Arch. f. klin. Chir. **186**:1-15, 1936.

8. Pusitz, M. E.; Owen, A. K.; Finney, G. A.; Lattimore, J. L., and Gerundo, M.: Osteomyelitis of Spine, J. Kansas M. Soc. **37**:265-287 and 313-324, 1936.

9. Wilson, J. C., and McKeever, F. M.: Bone Growth Disturbance Following Hematogenous Acute Osteomyelitis, J. A. M. A. **107**:1188-1193 (Oct. 10) 1936.

shaft of the bone was always present. Lengthening of the bone occurred in 21 per cent of the bones. The infections that resulted in lengthening were always situated in the diaphysis and left the epiphysial line undamaged. The same percentage of bones showed shortening, and this was the result of changes in the epiphysial line due to adjacent infection. Other deformities found were disturbance of the inclination of the joint in the hips, knee and ankle and a diminution in the size of the foot after infection higher up in the leg and thigh.

TUBERCULOSIS

A Survey of Tuberculosis of the Bones and Joints in Detroit's Municipal Sanatoriums.—Birkelo and Jarzynka¹⁰ present data to show that there is a marked decline in the incidence of tuberculosis of the bone. In 1929 there were 70 patients with osseous tuberculosis in the municipal sanatoriums of Detroit, which represented 6 per cent of all hospitalized patients with tuberculosis, while in 1933 and 1934 there were only 22 and 16, respectively, which represents 2 and 1.5 per cent for each of these years. This marked decrease is explained by the fact that osseous tuberculosis is usually secondary to a primary focus elsewhere, that this primary focus is being recognized earlier and that treatment is instituted sooner, thus preventing secondary complications. According to the authors, on the basis of population there was a higher percentage of Negroes with pulmonary tuberculosis in the city hospitals than of white persons and an even higher percentage of Negroes with osseous tuberculosis. Twenty-five per cent of the entire series of patients with osseous tuberculosis were Negroes. The location of the lesions in their respective order of frequency was as follows: spine, hips, knee, ribs, ankles, fingers, elbows, toes, wrists, sternum, shoulders, pelvis, clavicles, jaws and skull. Roentgenograms and a discussion of signs which lead to early diagnosis are included in the report.

Frozen Section Diagnosis of Tuberculous Joints.—Swift,¹¹ from a study of 175 patients suspected of having tuberculosis of the joints, arrived at certain conclusions as to the value of methods of diagnosing this condition, i. e., frozen section at the time of operation, paraffin section and inoculation of guinea-pigs. He found that frozen sections were not satisfactory in 18 per cent of cases and that paraffin sections showed tuberculosis in 23 of the 175 cases in which the diagnosis was not proved by frozen sections. Inoculation of guinea-pigs was done in 133 cases, and the diagnosis was proved 113 times. Swift emphasizes

10. Birkelo, C. C., and Jarzynka, F. J.: Survey of Bone and Joint Tuberculosis in Detroit Municipal Sanatoria, *Am. J. Roentgenol.* **36**:44-51, 1936.

11. Swift, W. E.: Frozen-Section Diagnosis of Tuberculosis Joints, *J. Bone & Joint Surg.* **18**:641-647, 1936.

(1) that satisfactory tissue must be taken for section; (2) that careful preparation of the frozen section is necessary and (3) that a careful inspection of the slides must be made.

[ED. NOTE.—In spite of the accuracy of diagnosis gained from tissue section and inoculation of guinea-pigs, in the vast majority of cases it is seen from Swift's figures and is known from experience that the clinical and roentgenographic aspects of the case must be considered. The experience and judgment of the surgeon at the time of operation is of the utmost importance in making the decision as to the question of fusion of the joint. In cases in which tuberculosis of the joint is suspected biopsy may not be necessary for diagnosis if the patient is observed for some time and if aspiration is used as a diagnostic method.]

Tuberculosis of the Hip in Children.—Barr¹² studied 106 consecutive patients with tuberculosis of the hip at the New England Peabody Home for Crippled Children. In 15 per cent it was later learned that an incorrect diagnosis had been made. Fifteen of the patients died—7 of tuberculous meningitis, 6 of secondary infection and amyloid disease and 2 of pulmonary tuberculosis. The disease was found to run a variable course, and cure was never certain, but the condition was frequently arrested. Arrest of the disease with a useful range of motion occurred too rarely to make it an expected result in the case in which conservative treatment is used. After long-continued conservative therapy to arrest the disease, operative fusion of the hip joint offered the best chance of a stable, weight-bearing limb.

Abscess of Firmly Ankylosed Tuberculous Hips.—Adams¹³ observed the development of a tuberculous abscess in 6 of 30 patients with tuberculosis of the hip on whom an operation has been performed previously. The abscesses developed after ankylosis of the hip occurred.

[ED. NOTE.—These papers show that one can never be certain of cure in cases of osseous tuberculosis. The disease may progress in a joint in which bony ankylosis has occurred.]

CHRONIC ARTHRITIS AND BURSITIS

Spondylitis Deformans of the Cervical Portion of the Spine.—From a study of roentgenograms of the cervical portion of the spine for 140 persons of varying ages admitted to the hospital for various reasons, Ober¹⁴ found positive evidence of spondylitis deformans in 57 per cent

12. Barr, J. S.: Tuberculosis of the Hip in Children, J. A. M. A. **107**:1517-1522 (Nov. 7) 1936.

13. Adams, Z. B.: The Occurrence of Abscesses from Tuberculous Hips That Are Firmly Ankylosed, J. Bone & Joint Surg. **18**:974-978, 1936.

14. Ober, G.: Ueber "Spondylitis deformans" der Halswirbelsäule, Deutsche Ztschr. f. Chir. **246**:666-684, 1936.

of those between the ages of 35 and 40 and in 85.7 per cent in the age group of 60 or above. No relationship was found between the extent of the roentgenographic change and the clinical symptom of pain. In 15.8 per cent of those with roentgenographic changes and in 6.5 per cent of those without roentgenographic changes subjective disturbances were recorded. The prodromal state of the lesion might make itself roentgenographically apparent with isolated calcification of the anterior ligaments, osteophytic formations at the point of attachment of the anterior ligaments or by deformity of individual vertebral bodies.

Arthritis and Injuries to Joints.—Kling¹⁵ calls attention to the value of examination of effusion from the joints both from a diagnostic and from a therapeutic point of view. He believes that there are definite diagnostic differences between traumatic and inflammatory effusion. If there has been recent trauma, the effusion may be hemorrhagic and contains a mucinous body, which he considers to be a secretory product. Fat globules may be present if the injury is severe. Centrifugation easily demonstrates their presence. Cytologic examination may reveal bone marrow cells in addition to the usual blood constituents. Kling points out that if the icteric index of the fluid is 5 or more, the effusion is traumatic or more rarely due to hemophilia, xanthoma, sarcoma or tabetic arthropathy. An inflammatory effusion has an index of less than 5. Fluid from hypertrophic arthritic joints shows a high viscosity with a small number of cells, chiefly monocytes and synovial lining cells. In villous arthritis over 15 per cent of the cells are synovial.

Transient Synovitis of the Hip Joint.—Finder¹⁶ reviews the histories of 22 children with transitory synovitis of the hip joint. The average age in his series was 5.4 years, the youngest patient being 11 months and the oldest, 14 years. The chief symptoms of this condition are pain, limp and muscular spasm. The temperature and white blood cell count may be elevated slightly. The tuberculin test and roentgenographic examination usually give negative results. The differential diagnosis includes tuberculosis, and a period of rest in bed under observation may aid one in making the diagnosis. The acute phase generally lasts from two to four weeks, and the treatment consists of rest in bed and traction or immobilization in a plaster spica. All the patients in Finders' series recovered completely.

Treatment of Subacromial Bursitis by Roentgen Therapy.—Lattman¹⁷ believes that roentgen therapy gives quicker relief from pain and

15. Kling, D. H.: Arthritis and Injuries to Joints, Arch. Surg. **33**:213-224 (Aug.) 1936.

16. Finder, Jerome G.: Transitory Synovitis of the Hip Joint in Childhood, J. A. M. A. **107**:3-5 (July 4) 1936.

17. Lattman, I.: Treatment of Subacromial Bursitis by Roentgen Irradiation, Am. J. Roentgenol. **36**:55-60, 1936.

an earlier restoration of function than any other method of treatment for subacromial bursitis. The usual dosage is about 350 roentgens. Twenty patients were treated; a brief history and the result of a follow-up study of from one to five years are given in tabular form regarding each patient. One treatment was usually sufficient. The immediate effect of the roentgen therapy was usually increased pain for about twenty-four hours, which was controlled with a sedative. After this there was rapid abatement of symptoms, with complete relief in many cases in one week. A calcified deposit was observed in 5 cases; in 3 the deposit disappeared completely in two months.

Treatment of Tennis Elbow.—Cyriax¹⁸ believes that the usual pathologic picture in tennis elbow is a tear at the periosteal attachment of the extensor carpi radialis brevis muscle to the lateral epicondyle. His method of treatment, which was successful in all but 1 of the 22 cases reported, consists of deep massage over the painful region with the elbow flexed at 90 degrees. This is followed by passive extension of the forearm to 180 degrees and forced adduction of the forearm on the arm. Anesthesia is not required, and the procedure is repeated at intervals of two or three days for four or five treatments. It may be used in recent or in old cases. The literature on tennis elbow is reviewed fully.

NEOPLASMS

Tumors of the Bone.—The second edition of the valuable work of Geschickter and Copeland¹⁹ contains the added result of a study of a large number of osseous neoplasms. The introductory portions on the interpretation of clinical findings by Dean Lewis and on diagnostic and therapeutic procedures by the late Joseph Bloodgood should be particularly helpful. The tumors of bone are grouped according to their derivation from embryonic or postembryonic types of tissue. The book is written in a clear manner and is well illustrated with reproductions of roentgenograms and photomicrographs. A well selected bibliography is added to each chapter.

Roentgenographic Stages in the Growth of Osseous Cysts.—Why do some simple osseous cysts yield readily to surgical intervention and others not? Fèvre²⁰ believes that the answer lies in the fact that some of the cysts are in an active growing stage and others in a quiescent,

18. Cyriax, J. H.: *The Pathology and Treatment of Tennis Elbow*, J. Bone & Joint Surg. **18**:920-940, 1936.

19. Geschickter, C. F., and Copeland, M. M.: *Tumors of the Bone*, New York, American Journal of Cancer, 1936.

20. Fèvre, M.: *Les étapes radiologiques dans l'évolution du kyste des os*, Rev. d'orthop. **23**:131-142, 1936.

stable state. He divides simple, benign cysts into three types. The first type is the growing cyst. This cyst is characterized by the total lack of any definite limit (in roentgenogram) at its diaphysial border. No line can be drawn between the margin of the cyst and the medullary canal. The cyst does not respond well to operation and is prone to recur. The second type is the stable or quiescent cyst. This cyst shows a definite lower limit consisting of a dense layer or shell of bone separating the cyst from the medulla. The cyst responds well to operation and does not tend to recur. The third type is the stable but enlarging cyst. This cyst is also stable, and while it does not tend to progress down the shaft of the bone, it enlarges in diameter. The cyst also responds favorably to operation. The author believes that these types of cysts represent different stages in development or growth, and he presents a series of illustrations to substantiate his opinion.

Surgical Treatment of Osseous Cysts.—Von Matolcsy²¹ reports on 48 cases of osseous cyst in which operation was performed at the University of Budapest. Curettement and packing with a tibial bone graft were employed in 45 of the cases. In 2 the grafts extruded. Healing occurred in all cases. In children before the cessation of the growth of bone reconstruction of the inserted graft progressed rapidly, identity of the graft in a child of 5½ being almost lost in eight or ten months. In an adult of 24, 2 tibial grafts inserted into the cyst neck of a femur reached approximately the same stage in from two to three years. The author fills the rest of the cavity left after insertion of the bone grafts with fat.

Treatment of Ganglions.—Saegesser²² reviews the more commonly used forms of treatment for ganglion. Rupture by a blow is not infrequently followed by a recurrence. Surgical extirpation is not a simple office procedure; it leaves a bad scar (unless the transverse incision is used at the wrist) and may also be followed by recurrence. Injection of irritating solutions often leads to recurrence and in addition may result in inflammation of the communicating joints. The recurrence is due to adjacent young cysts. The author recommends multiple punctures as practiced by Budinger. Through a single site in the skin a needle is inserted into the ganglion. Many punctures are made by partially withdrawing the needle each time. The base of the ganglion is particularly well perforated to destroy small growing cysts. The contents of the ganglions are extracted through the needle puncture, and heavy massage is applied to the site of multiple punctures. A pressure

21. von Matolcsy, T.: Ueber die chirurgische Behandlung von Knochencysten, Arch. f. klin. Chir. 185:175-181, 1936.

22. Saegesser, M.: Die Behandlung der Ganglien, Schweiz. med. Wchnschr. 66:663-664 (July 11) 1936.

pad is applied for eight days. After two weeks a hard lump remains. No recurrences have been observed by the author.

[ED. NOTE.—The method has been extensively practiced in America. One of the editors has observed recurrences but no more frequently than after excision or injection.]

THE BACK

Sacrarthrogenetic Telalgia.—Pitkin and Pheasant²³ suggest that the term "sciatica" is a poor one to apply to pain originating in the sacrolumbar and sacro-iliac regions. In place of it they would substitute the term "sacrarthrogenetic telalgia." A summary is given of the various points of view concerning the origin of pain low in the back with radiation down the extremity. Dissections on cadavers and on autopsy specimens confirmed Rudinger's observations as to the innervation of the lumbosacral and sacro-iliac articulations. The authors regard pain in the extremity when associated with discomfort low in the back as being a true referred pain and not due to irritation or compression of the trunks of the peripheral nerves. They state that pain is referred from the sacrolumbar zygapophysial articulations to the fourth and fifth lumbar posterior dermatomes; from the sacro-iliac articulation to the fifth lumbar and the first and second sacral posterior dermatomes; from the iliolumbar ligament to all of the five lumbar and first three sacral posterior dermatomes as well as to the first three lumbar anterior dermatomes; from the sacrolumbar and anterior sacro-iliac ligaments to the second and third lumbar anterior dermatomes, and from the posterior sacro-iliac and sacro-ischial ligaments to all of the five lumbar and first three sacral posterior dermatomes as well as the fifth lumbar and first three sacral anterior dermatomes. A study was made of sacral mobility. They found that motion in the sacro-iliac joint can be demonstrated during life and that the amount of motion in the ilia can be measured. In standing, all motion of the trunk, except flexion and extension, are associated with antagonistic movements of the ilia. In males complaining of sacrarthrogenetic pain an increase of one-third in the movement of the ilia was commonly found. The authors devised a special inclinometer to measure this motion. The problem of alternating scoliosis was next considered. They found 22 cases of this condition mentioned in the literature. Sixty-eight examples of alternating scoliosis were found

23. Pitkin, H. C., and Pheasant, H. C.: *Sacrarthrogenetic Telalgia*: I. Study of Referred Pain, *J. Bone & Joint Surg.* **18**:111-133, 1936; II. Study of Sacral Mobility, *ibid.* **18**:365-374, 1936; III. Study of Alternating Scoliosis, *ibid.* **18**:706, 1936. Pitkin, H. C.: IV. Differential Diagnosis in Sacrarthrogenetic Scoliosis, *ibid.* **18**:1008-1017, 1936; V. A Plan for Treatment, *ibid.* **19**:169-184, 1937.

in 506 examinations for pain low in the back with radiation as described. They believe that the scoliosis was the result of a fixed pathologic position of one or more of the upper sacral joints and that alternation of the scoliosis was caused by a change in the fixed pathologic position of one or more of these joints. The authors state that the sacro-iliac joints may be fixed in one of four pathologic positions: flexion, extension, an increased angle of inclination or a decreased angle of inclination. From these observations and from a statistical analysis of their cases, certain diagnostic postulates were made: 1. If the lumbar portion of the spine is normal, the lumbar curve reflects the position of the sacrum. 2. If the lumbar portion of the spine is normal and the lower extremities equal in length, the lumbar curve normally reflects the pelvic torsion. 3. Transitional sacroarthrogenetic scoliosis reflects the presence of unequal muscular action and denies the presence of sacro-iliac slip. 4. Structural sacroarthrogenetic scoliosis is produced by an iliac slip. 5. Functional sacroarthrogenetic scoliosis is produced by a sacral slip. 6. Secondary patterns of sacroarthrogenetic scoliosis are produced by a combination of slip and strain. Treatment of these disabilities should consist in the restoration of normal alinement in the sacro-iliac joints by relaxation and by manipulation. Normal articular alinement is reached when the back shows the transitional pattern of scoliosis. External support is advocated until normal muscular control is obtained. Where relaxation in the sacral joints persists, arthrodesis is advised.

Roentgen Treatment of Coccygodynia.—Baastrup²⁴ reports on the treatment of 15 patients with coccygodynia (8 with nontraumatic and 7 with traumatic coccygodynia) by roentgen therapy. Ten were satisfactorily improved (according to the author's standards, "well"). No unpleasant sequelae (premature climacterium) occurred. However, he advises that the treatment be restricted to women past the menopause and to men (whose testes may be shielded during irradiation).

VASCULAR DISORDERS OF THE LIMBS

Vascular Disorders of the Limbs.—A small volume by Thomas Lewis,²⁵ written particularly for the practitioner and the internist, should be of help also to the orthopedic surgeon who is often faced with functional disturbances resulting from faulty circulation. While nothing relatively new is reported, the book describes in simple language the

24. Baastrup, C. I.: Röntgenbehandlung von Kokzygodynien, Strahlentherapie 56:184-188, 1936.

25. Lewis, Thomas: Vascular Disorders of the Limbs, New York, The Macmillan Company, 1936.

present concepts of the dynamics and regulation of the circulation and their disturbances in disease. Many simple tests are given which can be carried out in the office without special apparatus. The various forms of treatment are discussed, with the benefit of the author's ripe judgment as to their efficacy.

DUPUYTREN'S CONTRACTURE

Dupuytren's Contracture.—Von Seemen²⁶ presents photographs of Dupuytren's contracture in a case in which excision of the fascia and involved skin was followed by application of a free flap of skin swung from the dorsum of the ulnar aspect of the hand (Lexer's operation). The author states that 10 patients have been operated on satisfactorily. For a while after operation there is a sense of tightening when a fist is made (glove sensation), but this subsides. The defect on the dorsum apparently cannot always be closed, and pinch grafts may be needed.

Reviewing the material of the clinic of Dr. E. Lexer at Munich, Maurer²⁷ collects 200 record cases of Dupuytren's contracture. He catalogs the other large series statistically. In his group the lesion was observed three times as often in men as in women. The lesion occurred in 2 patients under 10, in 27 between 40 and 50, in 50 between 50 and 60, in 65 between 60 and 70 and in 27 cases between 70 and 80. One hundred and ten of the patients, or 55 per cent, were hard-working hand laborers. Of the 200 persons afflicted, 49 suffered from muscular articular rheumatism, 18 from sciatica and 12 from gout. Eighteen patients had sustained injuries to the affected extremity. Of these injuries, only 1 involved the hand. Both hands were involved in 107 cases, the right in 52 and the left in 41. Of the 200 patients, in 12, or 6 per cent, the condition presumably had a familial basis.

MISCELLANEOUS

Stenosing Tenovaginitis at the Radial Styloid Process.—Burns and Ellis²⁸ find that stenosing tenovaginitis at the radial styloid process is more common in women than in men. There is usually a history of several months' increasing painful disability, and a swelling is noted in the line of the abductor pollicis and extensor pollicis brevis muscles. In some cases there is merely thickening of the sheath and in others

26. von Seemen, H.: Zur Operation der Palmarkontraktur (Dupuytren'sche Fingerkontraktur), Deutsche Ztschr. f. Chir. **246**:693-696, 1936.

27. Maurer, G.: Zur Lehre der Dupuytren'schen Palmarfascienkontraktur und ihre Behandlung, Deutsche Ztschr. f. Chir. **246**:685-692, 1936.

28. Burns, B. H., and Ellis, V. H.: Stenosing Tendovaginitis at the Radial Styloid Process, Lancet **1**:717-718 (March 28) 1936.

narrowing of the lumen. A partial excision of the sheath with the patient under local anesthesia has been found uniformly satisfactory.

Adhesion of Joints and Injury.—In the opinion of Watson Jones²⁹ stiffness of a joint after injury is due to adhesions of capsular plications. He states that adhesions following immobilization, if uncomplicated by other factors, recover by the patient's own exercise. This is particularly true of the elbow joint, which should never be subjected to massage or to passive stretching after injury. Other factors that might convert a recoverable stiffness into an irrecoverable stiffness are (a) disuse with continued venous stasis, (b) recurrent edema and (c) continued infection or irritation of foreign bodies near a joint.

Dystrophy of the Fifth Finger.—Thomas³⁰ reports 3 cases of dystrophy of the terminal phalanx of the fifth finger, which results in shortening and curving of the bone. He suggests that the change is due to osteochondritis. Kirner described this condition.

Hysterical Paralysis.—Myerson³¹ reports 6 cases of hysterical paralysis in which cure was obtained by various forms of suggestion. Electrical stimulation of the paralyzed muscles was of use in 2 of the cases. Primary anesthesia followed by directed activity of the patient was resorted to in 2 cases. Assisted motion of the affected member with liberal amounts of suggestion affected recovery in the other 2 cases.

[ED. NOTE.—Hysterical paralysis is not infrequently encountered by the orthopedic surgeon. A careful reading of this article will enable him to understand better the mechanics of production and the rational treatment of these interesting and bizarre states.]

ORTHOPEDIC OPERATIONS

Arthroplasty of the Knee.—Samson³² reports his results in 37 cases in which arthroplasty of the knee was performed. He has operated in 11 other cases in addition. Approximately one half of the operations were done for ankylosis following gonorrheal infections. All joints were quiescent for at least one year before operation. The usual Putti operation was modified to include construction of a tendon in the center of the joint to prevent lateral displacement of the joint. A free flap of

29. Jones, R. W.: Adhesions of Joints and Injury, Brit. M. J. **1**:925-929 (May 9) 1936.

30. Thomas, A. R.: A New Dystrophy of the Fifth Finger, Lancet **1**:1412-1413 (June 20) 1936.

31. Myerson, A.: Hysterical Paralysis and Its Treatment, J. A. M. A. **105**: 1565-1567 (Nov. 16) 1936.

32. Samson, J. E.: Arthroplasty of the Knee Joint, J. Bone & Joint Surg. **18**:881-892, 1936.

fascia lata is used. Elaborate physical therapy is not considered important, but early weight bearing and the development of muscular strength are emphasized.

Repair of the Ligaments of the Knee.—In a review of 183 cases of derangement of the knee joint, Campbell³³ found evidence of sufficient damage to the ligamentous structures to warrant operative repair in 30. There were 12 cases of rupture of the mesial (internal lateral) ligament and 19 cases of rupture of the anterior crucial ligament. The author describes a new method of repair of the anterior crucial ligament. The joint is exposed through a medial parapatellar incision, and whatever intra-articular repair is necessary is done. A pedicle strip $\frac{1}{3}$ inch (0.8 cm.) in diameter and 8 inches (20 cm.) in length is dissected from the quadriceps tendon, capsule and patellar tendon, leaving it attached to the tibial tubercle. A 6 mm. drill hole is then made in the tibia, beginning $1\frac{1}{2}$ inches (3.8 cm.) below the joint line on the anterior internal surface and emerging in the joint just in front of the spine of the tibia at the point of insertion of the anterior crucial ligament. The femur is then drilled, beginning in the intercondylar notch at the point of origin of the anterior crucial ligament and emerging on the lateral aspect of the femur. The free end of the fascia strip is threaded through these holes and securely inclosed in the fascia lata and periosteum after its exposure through a short second incision. The knee is immobilized for three weeks. There was one failure in the 18 cases. Campbell considers the operation simpler and less traumatic than the usual Hey-Groves procedure.

Operation for Ununited Fracture After the Method of Matti.—Matti,³⁴ of Bern, exposes the site of the ununited fracture and frees all of the contiguous ends of bone except a band (tibia) the width of the finger, posteriorly or laterally (on the femur), which serves to maintain position. The marrow cavity is exposed and chiseled back to bleeding marrow. The edges are freshened. Marrow and spongiosa are removed from the greater trochanter (or from the head of the tibia) and packed carefully between the ends of bone as a bridge from marrow above to similar marrow below. The cortical bone removed in the exposure of the marrow cavities is broken up into tiny pieces and is used to fill the cavity completely. Fixation by wire traction is used if necessary. Weight bearing is deferred until roentgenographic evidence of consolidation has appeared. Since 1926 the author has operated in 25 cases of ununited fracture (of the tibia in 12 cases, the femur in

33. Campbell, W. C.: Repair of Ligaments of Knee, Surg., Gynec. & Obst. **62**:964-968, 1936.

34. Matti, H.: Technic and Resultate meiner Pseudarthrosenoperation, Zentralbl. f. Chir. **63**:1442-1453 (June 20) 1936.

6, the radius in 3, the digital phalanges in 2, the clavicle in 1 and the metatarsus in 1). He obtained spongiosa fifteen times from the greater trochanter (flat approach or hollow chisel). Twenty-three operations have been performed by others. The results of this operation in the author's hands were uniformly successful, even in 2 cases in which infection developed. With the exception of these cases (consolidation in six months), consolidation was obtained in from six to twelve weeks. Of the entire group of 55 cases, union was obtained in 94.5 per cent.

Correction of Equinus.—Kofmann and Wassiliowa³⁵ contend that the usual tenotomy of the achilles tendon for the correction of equinus leads to permanent muscular weakness. They believe that a gradual correction in both flaccid and spastic paralyses can usually be obtained by gradual redressement. Where the equinus is resistant, a plastic lengthening of the aponeurosis of the gastrocnemius and soleus muscles permits correction of the deformity. This is performed through two lateral incisions at the junction of the upper and the middle third of the calf. The head of the gastrocnemius muscle is retracted posteriorly, and the aponeuroses over both the gastrocnemius and the soleus muscle are cut transversely. Occasionally the iliotibial band must also be incised just above the knees. This permits correction of the deformity. The foot is held in the corrected position in a plaster cast until healing occurs.

Reconstruction of the Digital Tendon Sheath.—Mayer and Ransohoff³⁶ describe their method for the restoration of the digital tendon sheath by the use of tubes of pyroxylin. The operation is done in two stages. The first consists in transplanting the tube after incision of the scarred tendon with its sheath. The tube is attached proximally and distally to the remaining tendon stump. At the second operation, performed from four to six weeks after the first, the tube is removed, leaving a well formed cellular sheath through which a transplanted piece of tendon is drawn and sewed to the tendon stump proximally and distally. The operative technic is carefully described.

FRACTURES AND DISLOCATIONS

Reversed Colles' Fracture.—Webb and Sheinfeld,³⁷ from a study of the literature and their own experience, conclude that the relatively rare reversed Colles fracture cannot be reduced successfully by closed

35. Kofmann, V., and Wassiliowa, N.: Die physiologische Korrektur des Spitzfusses, *Ztschr. f. Orthop.* 65:226-235, 1936.

36. Mayer, L., and Ransohoff, N.: Reconstruction of Digital Tendon Sheath, *J. Bone & Joint Surg.* 18:607-616, 1936.

37. Webb, G., and Sheinfeld, W.: Reversed Colles Fracture with Special Reference to Therapy, *J. A. M. A.* 104:2324-2326 (June 29) 1935.

manipulation and advocated open reduction as a routine procedure. Raymer³⁸ and Bettman and Tannenbaum³⁹ report 2 cases in which successful closed reduction was accomplished. Postreduction immobilization of the wrist in the neutral or dorsiflexed position was emphasized in both papers.

Conservative Treatment for Habitual Dislocation of the Shoulder.—Davis⁴⁰ reports 8 cases of recurrent dislocation of the shoulder, in 6 of which the treatment consisted of adhesive fixation and exercises. The fixation held the arm both forward and in adduction across the chest. Use in this position was permitted. Fixation was applied for two weeks, and exercises were continued for another month. The exercises were given with a view to overdeveloping the internal rotator and abductor muscles. The author offers suggestions as an alternative to operation and not as a substitute.

Dislocation and Fracture; Dislocation of the Elbow.—Biebl⁴¹ reviews 65 cases of dislocation and fracture dislocation of the elbow seen in the clinic of Dr. Lorenz Böhler. In 29 of the cases there was dislocation only, and in the remainder the dislocation was complicated by fracture of varying severity. The most common form of dislocation was posterior and to the radial side. Reduction was obtained by traction and manipulation with the patient under local anesthesia. The arm was then encased in plaster from the phalanges to the axilla, with the elbow at right angles and the forearm midway between pronation and supination. The plaster cast was usually left in place three weeks. The patients returned to work on the average in fifty days. Two had normal function. Myositis ossificans was observed in the brachialis internus muscle. This, the author believes, is due to therapy and is not the result of trauma. In 23 cases roentgenograms taken long after the injury showed ossification in the ligaments and capsule. The roentgenographic picture was normal in only 2 cases after the patient's discharge from the hospital. There were 6 instances in which dislocation was complicated by a tearing off of the medial epicondyle; all but 1 of these were in children. Bony union of the torn epicondyle was found in only 1 case; in spite of fibrous union, good function was obtained in every case. Fracture sprains of the supporting ligaments or of the tip of the olecranon were seen in 4 cases. Myositis ossificans or arthritis deformans was

38. Raymer, J. G.: Reversed Colles Fracture, J. A. M. A. **105**:2150-2151 (Dec. 28) 1935.

39. Bettman, R. B., and Tannenbaum, W. J.: Reverse Colles Fracture—A Plea for Closed Reduction, J. A. M. A. **105**:2151 (Dec. 28) 1935.

40. Davis, A. G.: A Conservative Treatment for Habitual Dislocation of the Shoulder, J. A. M. A. **107**:1012-1015 (Sept. 26) 1936.

41. Biebl, R.: Ueber Endausgänge traumatischer Verrenkungen und Verrenkungsbrüche des Ellbogengelenkes, Arch. f. orthop. u. Unfall-Chir. **37**:55-79. 1936.

not observed in any of these. Treatment of dislocation complicated by fracture was conservative in most instances; the arm was kept in a plaster cast from six to eight weeks. After removal of the plaster cast, active exercises were given. Massage and passive exercises were rarely used. Myositis ossificans was found in only 1 case of dislocation complicated by fracture. Of these 23 patients with fracture and dislocation, 12 have normal motion. Only 2 are still receiving compensation.

Fracture of the Ribs from Cough.—Since 1862, when Gurlt reported 14 cases of fracture of the ribs due to cough, others have reported similar cases, bringing the total to 90. Oechsl⁴² made a search for fracture of the ribs in the routine interpretation of 2,000 roentgenograms of the chest and found 11 instances in which from one to four ribs were fractured, an incidence of 0.6 per cent. In all cases the fracture was undoubtedly due to cough. The majority of patients had tuberculosis in the advanced stage. The appearance of the ribs were normal, and healing was prompt. The majority of the fractures were on the right side. The symptoms are typical: During a severe coughing spell a "catch" or "stabbing pain" is felt in a sharply localized area. The position of the fracture line is of considerable interest in relation to the mechanism of fracture. Without exception the fractures were found in a line extending from a point 4 cm. from the costochondral articulation of the fourth rib obliquely downward and laterally to the ninth rib in the midaxillary line. This location corresponds to the heavy muscular attachments of the external oblique muscle, where it interdigitates with the serratus anterior muscle. Anatomic and physiologic evidence indicates that the opposing action of the two sets of muscles, i. e., the serratus muscle against the abdominal muscles, causes these fractures.

Fractures of the Lumbar Transverse Process.—Decoulx and Patoir⁴³ report that fractures of the lumbar transverse processes are produced either by direct or by indirect violence. In a study of the observations of Chavannaz on 128 cases of fracture they found that 1 process was involved in 35 per cent of the cases, 2 in 29 per cent, 3 in 21 per cent, 4 in 9 per cent, 5 in 3 per cent, 6 in 2 per cent and 7 in 17 per cent. The injury occurred in the first lumbar process in 33 per cent, in the second lumbar process in 48 per cent, in the third lumbar process in 61 per cent and in the fourth lumbar process in 20 per cent. The displacement was always the same, outward and downward. The point is

42. Oechsl, W. R.: Rib Fracture from Cough, *J. Thoracic Surg.* 5:530-534, 1936.

43. Decoulx, P., and Patoir, G.: Les fractures des apophyses transverses lombaires, *Rev. d'orthop.* 23:97-120, 1936.

emphasized that injury to the soft parts is just as important as the bony lesion and is often responsible for most of the symptoms. The authors divide fractures of the lumbar transverse process into four groups: (1) the common type, (2) the benign type, (3) the masked type and (4) the grave type. In the common type pain is localized to the site of the injury, and no abdominal symptoms are present. Often roentgenograms are the only means of making a diagnosis. Almost no clinical signs are noted in the benign type, which usually consists of fracture of a single process with displacement. In the masked type few symptoms are present at first, the fracture being completely concealed by the presence of other lesions. Symptoms arise when the patient gets up and increase in severity. The symptoms in the grave type are severe. Abdominal rigidity and distention are present. Laparotomy is occasionally performed in cases in which this type of fracture is present. The abdominal symptoms are probably due to retroperitoneal hematoma. The clinical course of these fractures is variable. Isolated fractures may occur without displacement and give rise to few symptoms; in other cases the symptoms are marked. Some fractures with gross displacement give no more trouble than the simple fractures. This discrepancy is explained by a difference in the injury to the soft parts. Treatment consists of recumbency in bed for from two to four weeks. No plaster casts or leather jackets are used. Operation and removal of the fragment done either early or late are frowned on except in rare cases in which there is definite evidence of involvement of the nerve roots.

Treatment of Unreduced Dislocation of the Ankle.—Padovani⁴⁴ discusses in detail the treatment of old unreduced dislocations of the ankle accompanying malunited fractures about the ankle joint. He classifies the deformities in four groups: dislocations of the ankle backward, forward, inward and outward. These are the result of malleolar (or bimalleolar) fractures, supramalleolar fractures, epiphysial displacements and comminuted fractures of the lower end of the tibia. Treatment is discussed under the following headings: 1. Osteotomy at the site of fracture. This procedure is chiefly performed on one or on both malleoli. 2. Supramalleolar osteotomy. This operation is usually performed for supramalleolar fractures in which the ankle mortice itself is intact, but it is not necessarily performed at the exact site of injury. 3. Resection of the lower end of the tibia. This is done after comminuted injuries, and the aim is simply to place the astragalus in line with the tibia, irrespective of motion obtained. 4. Astragalectomy. This is performed only when none of the other methods seem applicable.

44. Padovani, M. P.: *Traitement des cals vicieux du cou-de-pied*, *Rev. d'orthop.* 23:441-489, 1936.

5. Arthrodesis of the ankle joint. This is used as an alternative to astraglectomy in selected cases.

[ED. NOTE.—A brief summary cannot do justice to this excellent, well illustrated article dealing with individual and difficult problems.]

End-Results of Fracture of the Distal Tibial Epiphysis.—Aitken,⁴⁵ from a study of 21 cases of injury to the lower tibial epiphysis, concludes that the type of injury to the epiphysis determines whether or not there will be subsequent disturbance of growth. He found that crushing of, or fracture through, the epiphysis usually results in a disturbance of growth even when the replacement of the epiphysis is perfect. Complete separation of the epiphysis from the diaphysis does not result in such disturbance even if replacement is not accurate.

RESEARCH

Interaction of Bone and Various Metals.—The interaction between bone and various metals has been investigated by Jones and Lieberman.⁴⁶ They found that vanadium steel and nickel-free rustless steel tacks were badly corroded both in bone and in Ringer's solution. High nickel and low nickel rustless steel tacks showed minimal corrosion, and much less bone reaction occurred about them than about any other alloys tested. The authors propose the hypothesis that the intensity of reaction of bone is directly proportional to the chemical changes that occur in the metal with which it is in contact. The question of whether a metal is irritating when buried in living tissue may be solved by immersing it in Ringer's solution; if it remains unchanged there it will probably do the same in vivo.

[ED. NOTE.—This work is of fundamental importance to all surgeons who use metal fixation material. The ordinary vanadium steel plates and screws cause marked irritative reaction and should be discarded in favor of alloys such as high or low nickel rustless steel, which are relatively nonirritating.]

Pathologic-Anatomic Investigation of the Cause of Osteogenesis Imperfecta.—Winkelmann⁴⁷ studied the histologic bone sections of a child who died of an infection of the respiratory tract while afflicted with osteogenesis imperfecta. He concludes that osteogenesis is imperfect in the sense that it is delayed but not impossible—simply incomplete. He draws the practical conclusion that if such children are protected

45. Aitken, A. P.: End Results of Fractured Distal Tibial Epiphysis, *J. Bone & Joint Surg.* **18**:685-691, 1936.

46. Jones, L., and Lieberman, B. A., Jr.: Interaction of Bone and Various Metals: Vanadium Steel and Rustless Steel, *Arch. Surg.* **32**:990 (June) 1936.

47. Winkelmann, K. L.: Pathologisch-anatomische Untersuchungen über das Wesen der Osteogenesis imperfecta, *Ztschr. f. Kinderh.* **58**:1-22, 1936.

from intercurrent infections of the respiratory tract they may be carried over the dangerous first years of life to become normal children.

[ED. NOTE.—No personal observations by the author are given to support such optimism. The editors have observed a greatly lessened tendency to fracture in the bones of these children after puberty.]

Distribution of Tension in the Neck of the Femur.—Küntsch⁴⁸ subjected the upper two thirds of a femur to pressure and measured the bending of the shaft at different levels with an instrument devised by Okhuizen. He found that the forces were not distributed uniformly, following instead definite paths. The paths are traced through the neck of the femur. The absolute elasticity of the bone substance is substantiated by measurement. Measurement in two axes is essential, for in the neck of the femur forces develop which are at right angles to each other. The author's curves are interesting. The absolute figures are not yet satisfactorily determined.

48. Küntsch, G.: Die Spannungsverteilung am Schenkelhals, Arch. f. klin. Chir. **185**:308-321, 1936.

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AUTOLYSIS OF TISSUE IN VIVO

AN EXPERIMENTAL STUDY WITH ITS CLINICAL APPLICATION
IN THE PROBLEM OF TRAUMA TO THE LIVER

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In any consideration of tissue autolysis, which means the destructive changes which take place in tissues disconnected from their blood supply, one is immediately impressed by two facts. First, most of the previous discussions on the fatal outcome have centered around the part played by *Bacillus Welchii*, or the gas bacillus. Second, the problem has been regarded almost entirely as an experimental one. In only a few of the excellent contributions to the subject is there even a hint of a possible clinical application. We disagree with both of these points of view. Our own experimental work has led us to believe that the rôle of the gas bacillus in the fatal outcome is an entirely secondary one. Our experimental and clinical work on the so-called "liver death" has led us to believe that the problem has a clinical aspect which heretofore has been almost entirely overlooked.

The gas bacillus in relation to tissue autolysis first appears in a contribution by Jackson,¹ of the Harvard Medical School. In 1909, after he had become interested in previous work on this subject by Lane-Clayton and Schryver, he undertook a series of experiments to determine the initial physical and chemical changes in organs disconnected from their blood supply. Lane-Clayton and Schryver had noted three distinct periods in tissue autolysis, a latent period, a rapid period and a gradual period, and Jackson was particularly interested in the latent period. He was able to show that this period is more likely to be present when the tissues have been temporarily cooled or when the percentage concentration of inorganic salts (calcium and potassium) in them has been changed by the use of saline solution. He demonstrated

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1. Jackson, H. C.: Effect of Conditions upon Latent Period and Rate of Aseptic Post-Mortem Autolysis During First Ten Hours, *J. Exper. Med.* **11**:55-83 (Jan.) 1909.

that lipolytic and amyolytic changes are operative in autolysis just as much as proteolytic changes; indeed, the lactic and higher fatty acids, which are present as the result of amyolytic and lipolytic changes, augment the proteolytic autolysis. Furthermore, the longer the tissue autolysis continues, the more marked is the depression of the freezing point, which implies, in turn, the breaking up of the molecules into smaller divisions. Finally, and most important for our purposes, Jackson found that the depression of the freezing point was most marked when there was present in the tissues an organism which resembled no organism heretofore known. It was never present at the end of six or eight hours, but it was uniformly present after twelve hours in liver tissue which had been removed with aseptic precautions, ground, placed in saline solution and incubated at 38 C.

Later in the same year this new organism was studied by Wolbach and Saiki,² who found it in the livers and spleens of all but two of twenty-three dogs but present in the kidneys and spleen (which had been removed for comparative purposes) of only one dog. We need concern ourselves only with their gross descriptions. At the end of forty-eight hours they noted that the sterile livers were fairly firm and elastic, with their color and odor practically unchanged, and no gas was present. The livers containing the new bacillus were dark grayish green on exposure to the air and bright red in the areas in contact with the dish. Crepitation was marked. The consistency was soft and plastic, and there was a strong odor, not putrefactive but peculiarly rancid or fatty. After from twenty-four to forty-eight hours the closed end of the fermentation tube was almost filled with gas. Filtrates of these livers injected into the peritoneum or the mesenteric vein produced no clinical or postmortem changes in experimental animals. Because these bacilli were invariably present in the livers which showed autolytic changes in vitro and invariably absent in the livers which showed no such changes, the authors concluded that they were responsible for the production of gas, the discoloration and the characteristic odor noted in these experiments, and, by inference, were responsible for the autolysis which occurred. In the light of the views we hold on the subject, we may fairly say that these deductions got the subject of liver autolysis off to a bad start.

Still later in the same year Jackson³ studied the sterile livers found in the experiments of Wolbach and Saiki and observed that after

2. Wolbach, S. B., and Saiki, T.: *New Anaerobic Spore-Bearing Bacterium Commonly Present in Livers of Healthy Dogs, and Believed to Be Responsible for Many Changes Attributed to Aseptic Autolysis of Liver*, J. M. Research **21**:267-275 (Sept.) 1909.

3. Jackson, H. C.: *Concerning Question of Rate of Autolytic Reaction and Appearance of Gases and Acids in Autolysis of So-Called Sterile Livers of Dogs*, J. M. Research **21**:281-284 (Sept.) 1909.

forty-eight hours the autolysis in them was comparable to the autolysis noted at the end of ten and twelve hours in the livers containing the new bacillus. This observation, in his opinion, further placed the responsibility for the autolysis on *B. Welchii*, as the organism was now called, and his conclusion, we believe, led later workers still further astray.

In 1927 Berg, Zau and Jobling⁴ repeated the work of Jackson, Wolbach and Saiki. They found the organisms in the liver tissue of all of their animals, though they were not present in the blood of the portal vein or in the bile of the gallbladder, an observation previously made by Wolbach and Saiki. In 1930⁵ Gage showed that the organisms reached the liver by way of the alimentary canal, passing from the duodenum probably by way of the common duct. The bacilli found on culture of the hair of dogs and the breasts of nursing animals were identical with the bacilli found in the stomach of these animals and in the stomachs of the puppies.

The problem of liver autolysis attracted little attention until 1925, when Mason, Davidson, Matthew and Rastello⁶ became interested in the use of heparin as an anticoagulant and sought some explanation of the widely varying reactions associated with its use. The method of its preparation suggested to them that liver autolysis might play some part in the results. It reminded them, too, of Mann's work, which showed that completely hepatectomized dogs lived longer than those with small amounts of liver substance free in the abdomen, and they sought to determine whether the autolysis in vivo of small amounts of liver tissue would liberate sufficient anticoagulant to be demonstrated by changes in blood coagulation. Their work stimulated further work on the subject, and since that time an elaborate series of experiments have been performed in various laboratories. These experiments, for purposes of clarity and convenience, we shall summarize in groups, under which we shall include the experiments which we ourselves have performed. Our comments and conclusions we shall reserve until later.

REVIEW OF EXPERIMENTS

1. *Implantation of Whole and Ground Liver.*—Mason and his associates, using fifteen dogs and employing the usual aseptic ritual, ligated one lobe of the host's liver and returned it free to the abdomen. All the animals were able to stand after operation and showed no signs of shock. Ten dogs died in from fifteen to eighteen hours, and none survived longer than seventy-two hours. Shortly before

4. Berg, B. N.; Zau, Z. D., and Jobling, J. W.: Bactericidal Function of Liver, *Proc. Soc. Exper. Biol. & Med.* **24**:433-434 (Feb.) 1927.

5. Gage, I. M.: Bacteriology of the Liver in Normal Dogs, *Proc. Soc. Exper. Biol. & Med.* **28**:257-259, 1930.

6. Mason, E. C.: Note on Use of Heparin in Blood Transfusion, *J. Lab. & Clin. Med.* **10**:203-207 (Nov.) 1924. Mason, E. C.; Davidson, E. C.; Matthew, C. W., and Rastello, P. B.: Study of Tissue Autolysis in Vivo: I. Blood Changes; Physical and Chemical, *ibid.* **10**:622-630 (May) 1925.

death, and with little warning, each animal turned on its side, with all four legs extended, respiration became labored, and death followed soon, with no struggle except the terminal one suggesting air hunger. Studies of the blood during life showed no significant changes in plasma volume, serum volume, fibrin, blood coagulation, amino-acids, sugar, urea nitrogen or uric acid.

The observations at postmortem examinations were invariably the same. The abdominal cavity contained from 100 to 300 cc. of brownish fluid, which was not actually blood. There was a pseudofibrinous exudate, which was easily removed. The intestines were markedly hyperemic and congested, as was the omentum, which was wrapped around the free liver. This liver tissue showed no gross characteristics of its origin. It was light chocolate in color and so spongy and crepitant that it had almost the feel of lung tissue. The ligated sections, which had weighed from 30 to 110 Gm. on implantation, had lost from 6 to 40 Gm. each.

Mason's experiments have since been repeated by Wangensteen and Waldron⁷ in the course of a series of experiments on the toxicity of various tissues autolyzed *in vivo*; by Haden and Orr⁸ in the course of a study of blood chlorides in proteose intoxication, and by Ellis and Dragstedt.⁹ The longest period of survival was that of a dog used by Wangensteen and Waldron, which lived for five days, and all the experimental work duplicated that of Mason. Ellis and Dragstedt, in addition to implanting the liver within the abdomen, also implanted it in the abdominal wall; a subcutaneous abscess developed, but the animal survived. Mason and Lemon,¹⁰ in similar experiments, endeavored to keep the animals alive by forcing fluids by various routes and by draining the peritoneal cavity. None of the animals survived longer than nineteen hours and twenty-five minutes, and the promptest death, in twelve hours and forty-five minutes, was that of the animal in which peritoneal drainage was done.

We repeated all of these experiments, using both whole and ground livers, always from other animals, for intraperitoneal implantation. All the animals died in from eight and a half to sixteen hours and presented the characteristic post-mortem changes.

2. *Implantation of Preheated Liver.*—Ellis and Dragstedt preheated the liver before intraperitoneal implantation to a temperature of from 75 to 80 C. for from fifteen to twenty minutes in an endeavor to destroy the autolytic enzymes. At the end of this period they were still able to culture positive anaerobic organisms from the tissues; death occurred from autolytic peritonitis in from twenty-four to thirty-six hours after implantation and the same organism was cultured after death. Dvorak¹¹ could not produce death by the use of simple boiled liver, though it invariably occurred if the liver was first incubated.

7. Wangensteen, O. H., and Waldron, G. W.: Studies in Intestinal Obstruction: IV. Strangulation Obstruction; Comparison of Toxicity of Intestine and Other Tissues Autolyzed *in Vivo* and *in Vitro*, Arch. Surg. **17**:430-439 (Sept.) 1928.

8. Haden, R. L., and Orr, T. G.: Blood Chlorides in Proteose Intoxication, J. Exper. Med. **48**:639-645 (Nov.) 1928.

9. Ellis, J. C., and Dragstedt, L. R.: Liver Autolysis *in Vivo*, Arch. Surg. **20**:8-16 (Jan.) 1930.

10. Mason, E. C., and Lemon, C. W.: Anhydremia as Possible Cause of Deaths in Liver Autolysis, Surg., Gynec. & Obst. **55**:427-431 (Oct.) 1932.

11. Dvorak, H. J.: Liver Autolysis in Peritoneal Cavity of Dog, Proc. Soc. Exper. Biol. & Med. **24**:431-434 (Jan.) 1932.

Repeating these experiments, we preheated the liver before implantation at a temperature of from 75 to 80 C. for two hours. All the dogs died in from forty to forty-five hours. We did not culture the livers before implantation, unfortunately, but we did recover the organisms postoperatively, and we noted the usual postmortem changes.

3. *Implantation of Autoclaved and of Incubated Liver.*—Ellis and Dragstedt autoclaved liver at a pressure of 15 pounds (6.8 Kg.) for fifteen minutes, after which they could not recover the organism, nor did death follow the implantation of these tissues. Dvorak added autoclaved liver to filtrates of incubated ground liver, and his dogs also survived. Andrews and Hrdina¹² implanted autoclaved liver, which had been proved sterile, in six dogs. Four died of autolytic peritonitis in from eighteen to seventy-two hours. One animal, killed in seventeen days, showed the implanted liver scattered throughout the abdomen and partially absorbed. Trusler, Reeves and Martin¹³ implanted finely ground autoclaved liver in seven dogs; one died of autolytic peritonitis in fifteen hours and another in eighteen hours; in the latter animal the implantation had been made in the abdominal wall through error. Another dog died of pneumonia in eleven days, but all the others survived. Dvorak's experiments also showed that autoclaved ground liver was not lethal. Andrews and Hrdina, who used autoclaved liver in a dog with jaundice and in another with a biliary fistula, produced autolytic peritonitis, but their results may perhaps be discounted in view of the preexisting pathologic process. Ellis and Dragstedt reinfected sterile autoclaved livers with organisms isolated in pure culture from fresh livers and invariably caused death in twenty-four hours, whether the implantation was done in the peritoneal cavity or in the abdominal wall.

In one of our experiments with unground autoclaved liver the animal died of autolytic peritonitis at the end of twenty-six hours, and the gas bacillus was recovered from the abdominal fluid. The other animals lived, whether ground or whole liver was implanted.

Andrews and Hrdina, and Trusler, Reeves and Martin, in various experiments with autoclaved, incubated liver, produced death in varying lengths of time, rarely over seventy-two hours, and typical postmortem changes were observed, though Trusler and his associates, in their elaborate bacteriologic studies, were not consistently able to obtain *B. Welchii* on culture. One dog in their series lived as long as six weeks, and then, as happens in the best of laboratories, was accidentally cremated before it could be examined.

Using 150 Gm. of ground, incubated liver, we produced autolytic peritonitis with death in nine hours. When the same amount of ground, incubated liver was autoclaved before implantation, death was deferred for thirty-six hours.

4. *Implantation of Various Sections of Liver.*—Mason and Nau,¹⁴ conceiving the idea that the exact section of liver implanted might alter the result, implanted the peripheral portion in a rabbit. When the animal was killed after sixty-seven hours no gas was present, but there was noted a small amount of free fluid in the

12. Andrews, E., and Hrdina, L.: The Cause of Death in Liver Autolysis, *Surg., Gynec. & Obst.* 52:61-66 (Jan.) 1931.

13. Trusler, H. M.; Reeves, J. R., and Martin, H. E.: Significance of Anaerobic Organisms in Peritonitis Due to Liver Autolysis, *Arch. Surg.* 30:371-393 (March) 1935.

14. Mason, E. C., and Nau, C. A.: The Cause of Death Due to Liver Autolysis, *Surg., Gynec. & Obst.* 60:769-774 (April) 1935.

abdomen, together with fatty degeneration of the liver, septic cholangitis and toxic parenchymatous degeneration of the kidneys. When the central portion of the liver was implanted, the rabbit died suddenly at the end of twenty-six hours, and the gas bacillus was cultured from the implanted liver.

We repeated these experiments with dogs. Whether the central or the peripheral portion of the liver was used, death occurred within eighteen hours from autolytic peritonitis, and *B. Welchii* was recovered from the peritoneal fluid.

5. *Implantation of Tissues Other Than the Liver.*—Using tissues other than the liver, we found that death occurred in twenty-six hours after implantation of the pancreas, in thirty-one hours after implantation of the heart with its valvular and vascular apparatus, in thirty-six hours after implantation of the lung and of the spleen and in forty-eight hours after implantation of the kidney. The only animal which survived was one in which only the heart muscle was implanted. It is worth mentioning that the animal which died the most promptly, the one in which the pancreas was implanted, was the only one on its feet the morning after operation, and its temperature, checked with three different thermometers, was 94 F., the lowest reading possible, four hours ante mortem.

Wangensteen and Waldron implanted various organs other than the liver, death occurring in a large proportion of the animals. They implanted the kidney in three dogs, with one death, and the spleen in twelve dogs, with eight deaths in an average of three and one-half days. Mason and his associates¹⁵ implanted the spleen in six dogs, with three deaths in from thirty-six to forty-five hours. No investigators, so far as we can determine, have used the lung or the heart except ourselves.

6. *Intraperitoneal and Intravenous Injection of Various Liver Extracts.*—Andrews and Hrdina injected intraperitoneally a concentrated extract of incubated liver, and death occurred in from seven to eighteen hours from autolytic peritonitis, although the same experiment with a less concentrated extract produced no perceptible effect. Our results from the intraperitoneal and the intravenous injection of liver extract, no matter what the degree of concentration and no matter whether or not the liver had been previously incubated, were all negative. Our conclusions are the same as those of Dvorak, i. e., that injections of aqueous extracts of ground, incubated liver that have been boiled are not fatal, nor are injections of ether or alcohol extracts of ground fresh liver. Dvorak's conclusion that the extract of incubated liver is fatal is in accordance with Andrews' results, but not with our own.

We lay no great stress on experiments with liver extracts. Any variation in preparation and concentration may result in a wide variation in results, and unless uniformity of preparation is certain, conclusions drawn from such experiments can only cloud the issue. For the same reason we are discarding the extensive experiments of Wangensteen and Waldron with various extracts in rats. It may be said, however, that in their work death occurred promptly in most cases, the brevity of survival being in inverse proportion to the length of incubation. The only rat which lived received a smaller dose than the others, and the extract was prepared after a much shorter period of incubation.

15. Mason, E. C.; Davidson, E. C., and Matthew, C. W.: Study of Tissue Autolysis in Vivo: III. Observations Using the Spleen, *J. Lab. & Clin. Med.* 10:997-999 (Aug.) 1925.

As early as 1925 Mason and his associates¹⁶ injected intravenously an extract of liver autolyzed in vivo and produced variations of a temporary character in the heart rate and blood pressure, even when pithed animals were used. Mason and Nau worked with rabbits. One showed no ill effects from the injection. The other was killed in five minutes and placed in the incubator for twenty-two hours. At the end of this time all the tissues were crepitant, and gas bacilli were cultured from the host's liver.

7. *Intraperitoneal and Intravenous Injection of the Peritoneal Exudate of Dogs Dying from Autolytic Peritonitis.*—Andrews, Rewbridge and Hrdina¹⁷ injected intravenously various fractions of the peritoneal exudate of dogs dying of autolytic peritonitis, without ill effect. On another occasion they introduced intravenously 240 cc. of the peritoneal exudate of a dog which had just died of autolytic peritonitis, again without ill effect.

We duplicated these experiments, with similar negative results. We also introduced intraperitoneally the entire peritoneal exudate of a dog which had just died of autolytic peritonitis, the animal surviving and seeming to be unaffected by the dose.

8. *Implantation of Various Culture Mediums and Bacterial Suspensions.*—We implanted in the peritoneal cavity of experimental animals both agar and sterile brain broth without effect. We also implanted anaerobic suspensions cultured from the peritoneal cavities of dogs in which various tissues had been implanted and death had occurred from autolytic peritonitis, again without effect. When anaerobic and aerobic suspensions from the same source were implanted, or aerobic suspensions alone, death followed within eighteen hours, although the picture was definitely not that of autolytic peritonitis. Streptococci, in some instances combined with staphylococci, and colon bacilli were regularly recovered from the peritoneal exudate. Dvorak produced death by the intraperitoneal implantation of an anaerobic suspension, although no results followed when the material was boiled before implantation. He noted also that death could be produced by the implantation of sublethal amounts of the bacterial suspension to which autoclaved ground liver had been added. Andrews and Hrdina made cultures of Welch bacilli from the peritoneum of dogs which died of autolytic peritonitis and injected the suspension into normal animals. The animals showed no reaction, and the peritoneal cavity was sterile when the four dogs were killed at the end of four days.

To show that the mere introduction of foreign substances has no deleterious effect, we introduced into the peritoneal cavity through a puncture wound 60 cc. of citrated blood from the animal's own femoral vein. No results of any sort were noted.

9. *Implantation of Fetal Liver.*—In 1930 Ellis and Dragstedt implanted in the peritoneal cavity fetal liver secured at cesarean section. In one animal only the liver was implanted; in another the entire abdominal viscera were added, and in the third the liver of a puppy which was infiltrated with a pure culture of anaerobic organisms was implanted. All the dogs remained well. When the abdomens of the animals were reopened at the end of twenty-six days there was no trace of the implanted liver in two of the dogs. In the third there was an intraperitoneal abscess containing pus from which anaerobic bacilli could be cultured, although

16. Mason, E. C.; Davidson, E. C., and Rastello, P. B.: Study of Tissue Autolysis in Vivo: II. Pharmacological Study of Toxic Material, J. Lab. & Clin. Med. 10:906-913 (July) 1925.

17. Andrews, E.; Rewbridge, A. G., and Hrdina, L.: Causation of Bacillus Welchii Infections in Dogs by Injection of Sterile Liver Extracts or Bile Salts, Surg., Gynec. & Obst. 53:176-181 (Aug.) 1931.

there was no trace of the implanted liver. Their conclusion was that the autolysis of sterile liver *in vivo* is not fatal.

We performed three experiments with fetal liver. In the first dog we implanted the livers of two puppies (35 Gm.) secured at cesarean section, and in the second dog we implanted the livers of four puppies (70 Gm.) secured at the same section. The first dog showed no effect of any sort. The second dog looked very ill for several days, then gradually recovered and remained well. In a third dog we implanted the livers of ten puppies (150 Gm.) secured at a single cesarean section. The dog got to its feet shortly after operation but was perceptibly droopy at the end of eighteen hours; it died three hours later, rather sooner than we anticipated. At autopsy the pathologic changes were typical of those due to autolytic peritonitis.

10. *Unduplicated Experiment.*—Using six dogs and implanting variously unground unautoclaved liver, unground autoclaved liver, ground unautoclaved liver and ground autoclaved liver, we also injected gas bacillus antitoxin into the animals, using it intraperitoneally, intramuscularly, intravenously or in a combination of these methods. Five of the animals died in from fifteen to forty hours, and on postmortem examination the pathologic changes were typical of those due to autolytic peritonitis. The sixth dog survived; 125 Gm. of unground, autoclaved liver had been implanted and 20 cc. of gas bacillus antitoxin injected intravenously. After being ill for several days, the dog seemed to recover completely. When its abdomen was reopened twenty days later there was no evidence whatever of a peritoneal reaction. The transplanted liver, which was completely encapsulated by omentum, was in excellent condition. It was our intention to reimplant it into another dog, but the laboratory porter, in an entirely atypical burst of cleanliness, threw it away with the sterile gauze in which it had been placed, and the plan could not be carried out. The host died some time later of natural causes.

COMMENT

This concludes, then, our own experiments and the more important of the previous experiments on tissue autolysis. What conclusions can be drawn from them? Before that point is discussed, one or two other facts should be emphasized. In the first place, we used dogs throughout, and our experimental work, therefore, has a sameness of background, as it were, which is disturbed in the experiments of others, it seems to us, by the occasional use of rabbits, guinea-pigs and rats as well as dogs. In the second place, our sterile technic was as flawless as we could make it, and we were careful in our last experiments to follow the plan of Trusler and his associates and hold the edges of the wound open as the liver was implanted. This method eliminates any possibility of contamination from the tissues of the abdominal wall, to which these workers are inclined to attribute the presence of the gas bacillus.

More important than these facts is the fact that the postmortem observations made in our experiments differ in one respect from those made by many other observers. We found, as they did, serosanguineous fluid in the abdominal cavity and congestion and hyperemia of the peritoneal surfaces, the intestinal tract and the omentum, which practically always encapsulated the implanted liver. We found, as they did, that the implanted liver had changed its form and appearance and had become

friable, gray and necrotic. But the change in the host's liver, especially stressed by Andrews and Hrdina, we noted only in cases in which autopsy was delayed. The observations of these authors in regard to the host's liver include gaseous crepitation, friability, a greasy feel and microscopic degeneration and necrosis, suggesting the picture of a severe toxic reaction rather than of a severe infection. When autopsy was delayed, as we have said, and particularly when it was delayed in hot weather, we noted these pathologic changes. When autopsy was done immediately, the host's liver was sometimes, though not always, congested and hyperemic, but it was never crepitant, friable or greasy, nor did it show marked microscopic evidence of degeneration. Earlier in the communication of Andrews and Hrdina occurs this statement: "In the vast majority of cases when the intraperitoneal injections or implantations were made in the afternoon, the animal was found dead and cold at 8 o'clock in the morning." This suggests that in this series, as well as in others in which their observations were duplicated, autopsy was delayed. It is our practice in experimental work to spend the night in the laboratory and to observe our animals at hourly intervals, remaining constantly with them if they seem on the point of death, so that autopsy is not delayed. We emphasize this point especially, for in other experimental work in which autolysis could play no part we have noted, whenever autopsy was delayed, the postmortem changes in the liver described by Andrews and Hrdina. Furthermore, we believe that the inconsistent findings of gas in the peritoneal cavity which are reported in various clinics can also be explained by delay in autopsy. When we opened the abdomen immediately after death, we never found gas, and only when unautoclaved or incubated liver had been used did we note the foul odor usually associated with the gas bacillus. When autopsy was delayed, gas was present, and associated with it always was the distinctive foul odor of the gas bacillus.

If the reports of the various experiments which we have summarized are carefully read, certain generally consistent results will be noted. It will be observed that when whole liver or ground liver was implanted, death followed rather speedily, especially when ground liver was used. This is true whether the liver was secured from the host itself or from another animal, in which case the factors of trauma, hemorrhage and shock naturally present in auto-implantation are entirely eliminated. It will be noted that death occurred at a longer interval when the implanted liver was first autoclaved and at a shorter interval when the implanted liver was first incubated. All of the animals which survived were animals in which autoclaved liver was implanted. It will be noted that death occurred regardless of what portion of the liver was

used. It will be noted that death occurred almost uniformly whether the liver or other tissues were used. We have already noted the variable results with liver extracts, and we think we may fairly refrain from further discussion of that point. It will be noted that in our own experiments, which were partially duplicated by other workers, death did not follow the implantation of anaerobic suspensions. It will be noted that the intravenous and the intraperitoneal injection of the peritoneal exudate of dogs which died of autolytic peritonitis caused no ill effects. It will be noted that our experiments with the implantation of fetal liver did not duplicate the experiments of Dragstedt and Ellis, in which the animals survived. It will be noted, finally, that in our experiments with implanted liver in which we used gas bacillus antitoxin in various doses and by various routes all but one of the animals died.

How are these conflicting results to be explained? Quite simply, it seems to us. In the first place, let us dispose of certain factors operative not only here but in other conditions. We noted, for one thing, that the resistance of the animal played some part, though not an important one, in the outcome. An animal which had been fed under our direction in our own animal house for several days before operation usually lived longer—and sometimes even survived—than an animal brought in from the street and operated on at once. This factor, however, we mention only tentatively, for too many other circumstances were associated to make it possible to advance it as an important consideration.

Again, the loss of blood volume resulting from the presence of free fluid in the peritoneal cavity, from the hemorrhagic infiltration of the omentum surrounding the implanted tissue and from the hyperemic and hemorrhagic changes in the mesentery and intestinal tract plays some part in the fatal outcome. These changes would be important under other circumstances, though here, again, other factors confuse the picture. The suddenness of death in these cases is very striking. The animal is up and moving about, apparently quite well. An hour or two later it is on its side, obviously very ill. A few minutes later it may be dead.

But these are minor considerations, and we mention them chiefly to eliminate them. They do not explain what happens in these experiments. That explanation lies along other lines. Previous investigators are of two opposite schools of thought. One school, represented by Ellis and Dragstedt, believes that the important consideration is the growth of bacteria in the autolyzing liver or other tissues. As Dragstedt¹⁸ pointed out to us in a personal communication, he is not con-

18. Dragstedt, L. R.: Personal communication to the authors.

vinced that "in the absence of bacterial growth in the necrotic tissue a toxemia can result." The other school of thought is represented by Andrews and his co-workers, who, curiously, are in the department of surgery at the University of Chicago, as is Dragstedt. Their conclusion is that in such cases "death is not due to a generalized peritonitis but rather to the absorption of toxic products generated from the liver tissue deprived of its circulation," and they have cited, in support of their idea, their experiments which show that the anaerobic bacilli found at the time of death may be injected intraperitoneally and intravenously without causing any harmful results.

All the experimental work that has been done, it seems to us, both in our own laboratory and elsewhere, points to the correctness of the latter point of view. We noted in our own experiments that death followed more quickly when ground liver was used than when unground liver was implanted. We noted that death followed more quickly when incubated liver was used than when unincubated liver was used. We noted that when autoclaved liver was used death was postponed and sometimes did not occur at all. Our conclusion from these observations is that while autolysis can occur under any circumstances with the implantation of liver, the latent period is prolonged by the use of autoclaved liver, sometimes so prolonged that the animal actually acquires a tolerance, as it were, and is thus able to escape death. When incubated liver is used, on the other hand, death is hastened, because the latent period is shortened or even eliminated, depending on the length of the incubation.

When whole, unground liver was used, death always occurred after a longer interval than when ground liver was used, and this also seems reasonable. Laying aside the possibility of cellular destruction and the faster liberation of autolytic enzymes, both of which are likely to occur when the liver is ground, it is logical to assume that the rate of autolysis and the consequent absorption of toxins will be faster because of the larger surface area. When the liver is used in a single piece, temperature changes occur more slowly, and disintegration of the outer surface must occur before the destructive process can extend inward, with the logical result that the absorption of toxins is retarded and death is deferred.

We noted almost invariably in our own experiments, though adequate data were missing for us to make the comparison with the reported experiments of others, that there was a definite relationship between the size of the dog and the amount of implanted liver. A small dose in a large dog meant a longer duration of life than the same dose in a smaller dog. An animal in which 100 Gm. of liver was implanted, for instance, lived sixteen hours, whereas an animal of the same size in which 150 Gm. was implanted died in eight and one-half hours.

This relationship was always definite and unmistakable, and it is most perfectly exemplified in our experiments with fetal liver. All three hosts were approximately the same size and weight. When a small amount of liver (35 Gm.) was implanted, there was no perceptible effect. When a larger amount (70 Gm.) was implanted, the animal was obviously ill but was able to take care of the toxemia. When a still larger amount was used (150 Gm., the amount used in most of our other experiments), the result was exactly as it was when adult liver was implanted, a quick death with a typical picture of autolytic peritonitis.

The fatal effect of the implantation of tissues other than the liver can be explained by exactly the same reasoning we have just set forth. It is significant that the only animal which survived in this particular series of experiments was a large dog in which only the heart muscle (75 Gm.) was implanted. When the heart was implanted with its vascular and valvular supply (100 Gm.), death followed quickly.

Our own idea of the rôle of the gas bacillus in autolytic peritonitis is that it is entirely secondary. Of its importance there can be no question. It is impossible to eliminate it entirely. But it is the autolysis, in our opinion, which produces the fatal results, and not the presence of the gas bacillus. This is proved conclusively, first of all, by our experiments with autoclaved liver and by the experiments of others. Some of the dogs lived, but some of them died. If the elimination of the gas bacillus were the important factor most investigators believe it to be, all of the dogs should have lived, and all of them did not, either in our own series or in any other series. The fact that autolysis occurs less speedily after autoclaving the liver and more speedily after incubating it we explain by the duration of the latent period, which is prolonged in the first instance and shortened or eliminated in the second, rather than by the presence or absence of the gas bacillus. It should be remembered, in this connection, that whenever the peritoneal fluid was cultured after death, whether the autolytic peritonitis had been produced by autoclaved or nonautoclaved liver, the anaerobic organism was present. Yet the injection of this fluid, intravenously or intraperitoneally, did not reproduce the pathologic change, which it should have done, it seems to us, if the rôle of the organism were as important as it is assumed to be. It must be remembered, furthermore, that we were unable to reproduce autolytic peritonitis by the intraperitoneal injection of anaerobic suspensions. In Andrews and Hrdina's similar experiment, just as in ours, the peritoneal cavity was always sterile after death; it should not have been if the gas bacillus has the potency it is supposed to have.

Our own experiments show that the use of gas bacillus antitoxin cannot stave off the fatal outcome in autolytic peritonitis, regardless of the method of administration or of the dosage used. The single animal which survived in our series was a large dog, in excellent condition, in which 75 Gm. of autoclaved liver was implanted in a single piece. All the circumstances were favorable: a large dose, a small amount of implanted liver, good resistance, slow absorption because of the smaller surface area and a longer latent period because of the previous autoclaving. The use of the gas bacillus antitoxin had little or nothing to do with his survival, we are sure. The circumstances for survival were simply more favorable than in the other dogs in this group. The results with gas bacillus antitoxin are so uneven that this argument is another one we use only tentatively, but it does seem that if the gas bacillus itself were at fault the use of the antitoxin might have showed results in one or two animals.

The most important proof of the whole matter, to us, lies in our experiments with fetal liver. Clearly, as we have pointed out, it was the amount injected in those experiments which made the difference. The livers were all sterile, and all were secured and implanted with hyperaseptic precautions. The animals were all the same size and in the same condition. Only the amount of implanted liver was the variable factor. When a small amount was implanted, there was no result. When a larger amount was implanted, there was a perceptible though not a lethal effect. When a still larger amount was implanted, the animal died of autolytic peritonitis. Ellis and Dragstedt's own experiments, for that matter, go to prove our point. If the tissue autolysis is bacterial, why did not the animal die in which they implanted a fetal liver infected with a culture of *B. Welchii*? The explanation of their negative results, in our opinion, is not the absence of bacteria but the small amount of liver implanted. We do not know the size of their experimental animals, but we do know that a fetal liver, even when all the abdominal viscera are added, weighs very little.

Our own idea is that the presence of the gas bacillus in tissue autolysis is important only in that it hastens the process of autolysis by acting as a catalyst. Its absence, whether achieved by autoclaving or occurring normally, slows up the process by prolonging the latent period, sometimes to such a degree that the animal is able to survive. Incubation has the reverse effect; by increasing the activity and the number of the organisms, it hastens or eliminates the latent period, and death follows quickly. This theory is supported by Jackson's original observation, the significance of which has either been entirely overlooked or incorrectly interpreted. He noted in his experiments on tissue autolysis that when the gas bacillus was present there was a more rapid depression of the freezing point, a process which is dependent on and

coupled with the rate of formation of the more simple protein molecules. He noted further that when the gas bacillus was present, the rate of autolysis at the end of ten and twelve hours was comparable to the rate of autolysis after forty-eight hours when it was not present. The clue to the problem has been at hand all these years, we believe, but it has been overlooked up to this time.

CLINICAL CONSIDERATION

Turning to the clinical aspects of the problem, we note that for some time there has been an endeavor to associate the gas bacillus as an etiologic agent with such clinicopathologic states as intestinal obstruction, acute appendicitis and trauma of various sorts, though so far most uneven results have followed the use of gas bacillus antitoxin. We wonder whether in those states the important consideration is not tissue autolysis rather than the gas bacillus antitoxin. Gangrene of the appendix involves tissue autolysis. Strangulation obstruction and subsequent gangrene involve tissue autolysis. Trauma to tissue involves tissue autolysis. Is it not likely, in all of these states, that the emphasis has been placed on the wrong thing? Is it not likely that the toxemia associated with them is due primarily to the presence of tissue disconnected from its blood supply and undergoing autolysis rather than to the presence of the gas bacillus? If our theory is correct, the uneven and unsatisfactory results of gas bacillus antitoxin are easily explained; it can have no effect on a toxemia produced by the autolysis of tissues.

These pathologic states have been considered by other observers, however, even if not exactly as we have considered them. We desire to turn our attention now to another clinical problem which so far has been entirely overlooked, the significance of tissue autolysis in cases in which the liver has been subjected to trauma.

Not with the idea of making a statistical report but solely from this aspect we have studied the records of patients with injury to the liver who were treated at the Charity Hospital in New Orleans for the last ten years. There were ninety-eight cases in all, with sixty deaths. In only fifty-four cases, however, with twenty-six deaths, a mortality of 48.1 per cent, was the liver alone involved, and the other cases we have eliminated from our discussion. The damage to the liver in them may have played a part, perhaps an important part, in the morbidity and mortality, but since injuries to other structures complicated the picture, we have preferred to analyze only the cases in which trauma to the liver alone was responsible for what happened.

In the whole group of fifty-four cases, thirty-nine injuries followed gunshot wounds, with eighteen fatalities; seven were due to stab wounds, with one fatality, and eight were due to rupture, with seven fatalities

Obviously stab wounds of the liver are the least fatal form of injury, and ruptured wounds the most dangerous, which is entirely in accord with our theory that the actual destruction of the liver tissue plays a much larger part in these cases than is generally realized.

While it has nothing to do with our point, it may be of interest to note that, as usually happens in this community, most of these patients were Negroes. The thirteen white patients, two of whom were females, were usually innocent by-standers or innocent victims of accidents. The Negroes, twenty-nine of whom were males, furnished, as always, the bulk of the patients. Oberhelman and LeCount,¹⁹ in a study of gunshot wounds, mentioned the contribution of American surgeons to this problem and particularly the contributions of Southern surgeons, who have always had the Negroes on their doorsteps. On the other hand, with the increasing use of automobiles and of heavy modern machinery, crushing injuries of the abdomen are increasing in number and need to be seriously considered.

Wounds of the liver are always serious. According to Vance's²⁰ figures, 33.3 per cent of such injuries are immediately fatal from shock and hemorrhage. Another 38 per cent result fatally within six hours, and treatment is impossible. In his series only 28.6 per cent of the patients lived long enough for clinical observation, and of these only 10 per cent were in shape for surgical treatment, which means, if the figures are generally applicable, that 90 per cent of such patients die before the surgeon has any chance to save them. According to Robertson,²¹ at the Guthrie Clinic no patient with a severe injury to the liver has lived long enough to be taken to the operating room.

Of eleven patients treated conservatively at the Charity Hospital, the diagnosis of trauma to the liver was only presumptive for the four who survived. The history and clinical course suggested damage to the liver, but it could not be proved. In the seven patients, or 63.6 per cent, who died, the diagnosis was proved by postmortem examination at the coroner's office, where, unfortunately, autopsy is performed in most of these cases, which prevents the intimate observation that this subject, in our opinion, gravely needs. In the forty-three cases in which operation was done, with nineteen deaths, a mortality of 44.2 per cent, the diagnosis was proved both by operation and by autopsy.

Of the patients who lived, eight were treated by suture of the liver, against none in the group who died. One patient was treated by suture

19. Oberhelman, H. A., and LeCount, E. R.: Peace Time Bullet Wounds of the Abdomen, *Arch. Surg.* **32**:373-412 (March) 1936.

20. Vance, B. M.: Subcutaneous Injuries of Viscera: Anatomic and Clinical Characteristics, *Arch. Surg.* **16**:631-679 (March) 1928.

21. Robertson, H.: Visceral Wounds Due to Trauma Where Abdominal Wall Has not Been Perforated, *Am. J. Surg.* **14**:395-418 (Nov.) 1931.

with muscle, against two in the group who died. Seven patients in the group who lived were treated by simple exploration, against three in the group who died; in the former group nothing more was done because it was not considered that anything more was needed, and the decision was correct; in the latter group, that decision was clearly in error in two cases, while in the third case nothing was done as a matter of necessity, it being impossible to check the bleeding by any method. In three patients in the group who lived and in four in the group who died it was impossible to tell what had been done; our conclusion is that no surgical treatment was attempted, for the reasons we have just set forth. Finally, in a double injury in a fatal case, both suture and pack were resorted to. It is perhaps of significance, even though the series is too small to draw conclusions from, that eight patients on whom suture of the liver was performed recovered, while the method was not employed on a single patient who died.

In the fatal cases in which surgical treatment was employed the causes of death included peritonitis in three, in two of which pneumonia was a factor; shock and hemorrhage in six; pneumonia in one; infection with gas bacilli, probably introduced with the bullet, in one; sepsis in one, and what we term "liver death" in seven, in one of which hemorrhage was also a factor.

We have been interested in collecting from the literature reports of the so-called liver death after trauma to the liver. The first case was reported by Furtwaengler²² in 1927, from Clairmont's Clinic in Zurich. The second was reported by Stanton²³ in 1930. The third was reported by Helwig and Orr²⁴ in 1932. Autopsy was not performed in Stanton's case but was performed in the two cases reported by the other authors, and in each there was found, in addition to a traumatic necrosis of the liver, a high grade bilateral necrosis of the cortex of the kidneys.

In the cases which we are reporting, six of which we have previously reported,²⁵ autopsy in the hospital was permitted in only two cases, in each of which the liver had ruptured. In the other cases, however, the clinical course was absolutely typical of the liver-kidney syndrome, the axillary temperature rising to from 105.4 to 108.2 F. In two cases the surgeon's notes mention the high grade necrosis of the

22. Furtwaengler, A.: Diffuse Rindennekrose beider Nieren nach Leberruptur, *Krankheitsforschung* 4:349-374, 1927.

23. Stanton, E. M.: Immediate Causes of Death Following Operations on Gallbladder and Ducts, *Am. J. Surg.* 8:1026 (May) 1930.

24. Helwig, F., and Orr, T. G.: Traumatic Necrosis of the Liver with Extensive Retention of Creatinine and High Grade Nephrosis, *Arch. Surg.* 24:136-144 (Jan.) 1932.

25. Boyce, F. F., and McFetridge, E. M.: So-Called "Liver Death": A Clinical and Experimental Study, *Arch. Surg.* 31:105-136 (July) 1935.

liver found at operation, and in a third case, in which operation was done six days after the injury, it was specifically stated that there was no trace of peritonitis at the time. By presumption, it seems to us, these cases can fairly be classified as examples of "liver death."

In each case of rupture of the liver immediate exploration was done. The clinical course was at first smooth, but later uremic symptoms were apparent. In one case profound jaundice followed, the icteric index reaching 210. Autopsy in each case revealed typical degenerative changes within the liver and kidneys, in one instance so extensive as to suggest acute yellow atrophy.

We believe that this syndrome explains the case of hepatic liver reported by Allen:²⁶ A white man 53 years old was struck by a sledge hammer thrown from a passing train. At operation the abdomen was full of blood, and there was a rupture 3 inches (7.6 cm.) long in the dome of the liver. Autotransfusion was done with the removed citrated blood. The patient was in good condition at the end of the operation but died with complete anuria fifty-six hours later. Although noting that the anuria may have been due to other causes, Allen attributed it to the intravenous administration of blood possibly mixed with bile. In our opinion autopsy would have showed typical changes in the liver and kidneys.

It is quite evident from these few cases that after trauma to the liver, exactly as after operations on the gallbladder, and, as we are coming to believe, after any operation on a person with a damaged liver, there may occur a distinctive syndrome. In life it is characterized by hyperpyrexia, with or without associated uremic symptoms, depending on the duration of the illness. At postmortem examination there are found degenerative changes within the liver, associated with renal changes of the same character if the patient has lived long enough. As Helwig and Orr have pointed out, and as we ourselves have observed, when death follows traumatic necrosis of the liver, the hepatic changes are limited to the traumatized area, whereas in nontraumatic states the degenerative changes are diffuse. In either state the damage to the kidneys is generalized.

If our theory of hepatic necrosis as an important if not the most important consideration in trauma to the liver is correct, our outlook on injuries to the liver must be radically changed. Our view is that of Fairchild,²⁷ who classified injuries of the abdominal viscera as conditions which demand immediate exploration, on the basis of our inability

26. Allen, A. W.: *Internal Abdominal Injuries Without Penetrating Wounds*, New England J. Med. **205**:34-38 (July 2) 1931.

27. Fairchild, F. R.: *Serious Intra-Abdominal Trauma Without External Evidence of Violence*, Surg., Gynec. & Obst. **52**:767-775 (March) 1931.

to say that certain lesions do not exist rather than that they do. If an error must be made, he added, surgical treatment is a procedure in which it entails the least fatal consequences. Eliason and McLaughlin,²⁸ speaking of penetrating wounds, made the same point. The surgeon has no right merely to hope, they said, that the injury has not caused hemorrhage or perforation. It is true that certain surgeons, Hinton²⁹ and Willis³⁰ for instance, have achieved excellent results in treating abdominal injuries conservatively, but we question the wisdom of a uniform adoption of their plan.

One point which surgeons who advise against conservative treatment would do well to bear in mind is made by Prey and Foster,³¹ in a report from the Denver General Hospital. In their series the average operating time in the fatal cases was one hour and ten minutes, only four consuming less than an hour. In the cases in which the patient survived, the average operating time was fifty-five minutes, and in none was the duration over an hour. Evidently speed in operating plays an important part in the results.

We might add at this point that in none of the patients we have observed or studied was brachycardia present. Almost without exception the patients had pulse rates that were more rapid than normal, sometimes considerably more rapid. Krieg³² and Wangensteen³³ also warned against trusting this sign, and it is evident that the original observation was not correct.

Exploration, we believe, should be undertaken in every case in which injury to the liver is suspected in which the patient is not actually moribund or in which he can be brought out of his shock and rendered fit for exploration. Transfusion is important in view of the enormous loss of blood which the double blood supply of the liver, from the hepatic artery and the portal vein, makes almost inevitable. Mason,³⁴ in a discussion of subcutaneous injuries of the abdomen before the American Surgical Association in 1933, called attention to the difficulty

28. Eliason, E. L., and McLaughlin, C. M., Jr.: Surgical Emergencies of Abdomen, *M. Clin. North America* **18**:63-80 (July) 1934.

29. Hinton, J. W.: Injuries to Viscera: Their Relative Frequency and Their Management, *Ann. Surg.* **90**:351-356 (Sept.) 1929.

30. Willis, B. C.: Shotgun Wounds of the Abdomen, *Am. J. Surg.* **28**:407-427 (May) 1935.

31. Prey, D., and Foster, J. M.: Gunshot Wounds of the Abdomen, *Ann. Surg.* **99**:265-270 (Feb.) 1934.

32. Krieg, E. G.: Hepatic Trauma, *Arch. Surg.* **32**:907-914 (May) 1936.

33. Wangensteen, O. H.: Abdominal Injuries, *Internat. Surg. Digest* **21**:323-335 (June) 1936.

34. Mason, J. M., in discussion on Lewis, D., and Trimble, I. R.: Subcutaneous Injuries of the Abdomen, *Tr. Am. S. A.* **51**:206-218, 1933.

of securing blood for indigent and friendless Negro patients and stressed the necessity of adopting some systematic measures for emergency transfusion. We echo his ideas, for the problem is one which we meet constantly at the Charity Hospital and against which we can fairly charge more than one personal fatality.

After the abdomen is opened, the procedure should depend on the findings. Abrasions and insignificant injuries do better, as this small series proves, if they are left untouched; suture or packing would simply introduce unnecessary trauma. An extensive laceration or deep wound should be sutured, if that is possible—suture of the liver, as Robertson notes, must be classed among the finer arts—otherwise the wound should be packed. Dragstedt and others have pointed out the damage which can be wrought by packs, their idea being that the pathologic change is obstructive. While this is undoubtedly true, we would emphasize the element of further trauma to the hepatic tissue which can be achieved by tight packing and the possible risk of hemorrhage when the pack is removed. We would also warn against the assumption that simply because a blood clot covers the wound no further bleeding is likely to occur. Unless the depth and character of the wound are known, this is a doubtful assumption, as is proved by the number of secondary hemorrhages noted in our small series of cases and in those reported in the literature. Even a slight rise in blood pressure as the patient comes out of shock may cause such a result.

In cases of extensive wounds in which there is extensive necrosis of the hepatic tissue, we take the position, we believe for the first time, that resection of the involved area best serves the patient's interests. We are quite aware of the risk of cutting into the liver, but we are equally aware, through our experimental and clinical studies, of the dangers of hepatic necrosis. Resection of the liver will always be a serious operation, never to be resorted to lightly and without due thought. But it is a perfectly feasible operation in view of the regenerative properties of this organ. Control of hemorrhage will always be difficult, but methods have been devised by which it can be achieved.

Tinker's ³⁵ report before the American Surgical Association in 1935 brought together, as it were, the possibilities of resection of the liver, and he emphasized, as we do, that when the necessity exists, the operation can be done. We are merely extending his indications. In a paper of our own on primary carcinoma of the liver ³⁶ we cited reports of

35. Tinker, M. B.: Liver Resection: Case Report and Advantages of Radio-cutting, *Tr. Am. S. A.* **53**:247-260, 1935.

36. Boyce, F. F., and McFetridge, E. M.: Primary Carcinoma of Liver, with a Report of Twenty-Eight Additional Cases, *Internat. Surg. Digest* **18**:67-80 (Aug.) 1934.

several such cases collected from the literature. Yeomans, for instance, performed a second operation for recurrence of this condition seven years after the original growth had been removed. Jackson did a resection of one of the lobes of the liver in a white woman 80 years old who was alive and well seventeen months later. Tinker quoted the experimental work of Fishback, at the Mayo Clinic, which shows that complete regeneration of the liver occurs within six to eight months after four fifths of it has been removed.

The operation, then, is entirely possible. As to the justification, we believe that the case reported by Fabricius Hildanus in the early part of the seventeenth century proves our point. A young man was stabbed in the abdomen and had a severe hemorrhage, which did not prove fatal. Some days later a large piece of liver appeared in the abdominal wound and was removed by forceps. *In spite of this fact*, said Shedden and Johnston,³⁷ who cited the case, he recovered. *Because of this fact*, we say, his life was saved. By autosurgery, as it were, the products of liver autolysis, which otherwise would probably have killed him, were eliminated from his body.

SUMMARY

We have reviewed previous experimental work on tissue autolysis and have added to it duplicated and original experiments of our own.

From our own experiments and the experiments of others we have concluded that in such cases the products of the autolysis are responsible for the fatal outcome and that the rôle of the gas bacillus is secondary and catalytic. We have pointed out also the effect of the size and condition of the experimental animal and the amount and form of the implanted liver, as well as the effect of autoclaving and incubating the tissue before implantation.

We have pointed out the clinical application of tissue autolysis in such pathologic states as gangrene of the appendix, strangulation obstruction and trauma to tissue.

We have applied our work on tissue autolysis specifically to trauma to the liver and have pointed out the important part which the destruction of hepatic tissue may play in the final result. In this connection we have collected reports of four cases from the literature, in two of which the diagnosis was proved by autopsy, and have added seven of our own, in two of which the diagnosis was proved by autopsy.

We have proposed, in the light of our theory of the danger of tissue autolysis, that exploration be done in all cases in which trauma to the liver is suspected and that resection be undertaken if the necrosis of the hepatic tissue is extensive.

37. Shedden, W. M., and Johnston, F.: Traumatic Rupture of the Liver, New England J. Med. **213**:960-964 (Nov. 14) 1935.

ACUTE PHLEGMONOUS ENTERITIS

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MacCallum¹ in 1906 reported a case of acute phlegmonous inflammation of the small intestine and reviewed reports of seven similar cases from the European literature. Since his article, the report of one other case has appeared in the American literature (Jones²), and it has been possible for us to collect and analyze reports of thirty-two additional cases of this disease that have been described in the foreign literature.

Two examples of this condition were recently seen at necropsy at the Bellevue Hospital. They are presented below, and the previously reported cases are reviewed.

REPORT OF CASES

CASE 1.³—J. M., a 46 year old white man, was admitted to the third medical division of the Bellevue Hospital on June 12, 1935. He was a vagrant and suffered from chronic alcoholism; his history was contradictory and unreliable. It was ascertained, however, that about twenty-four hours before his admission to the hospital he had become acutely ill with cramplike pains in the upper part of the abdomen, vomiting, chills and diarrhea. On physical examination he was retching and vomiting. There was diffuse tenderness, more marked on the left side of the abdomen, but there was absence of rigidity. The temperature was 103.2 F., the pulse rate 104, the blood pressure 164 systolic and 94 diastolic (in millimeters of mercury) and the white blood cell count 18,500, with 46 per cent polymorphonuclear leukocytes, 44 per cent metamyelocytes II and 5 per cent lymphocytes.

The following day the patient was delirious and tremulous. His abdomen was resistant, the rigidity being more marked on the left side. There was an ill defined mass, about the size of an orange, in the left lower abdominal quadrant. During the subsequent four days he remained acutely ill, although the vomiting and diarrhea ceased. The temperature fluctuated between 103 and 105 F. A soft mass became palpable in the left upper quadrant and to the left of the umbilicus, which was interpreted as the spleen by some observers. Two blood cultures proved sterile. Death occurred on June 17.

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1. MacCallum, W. G.: Phlegmonous Enteritis, *Bull. Johns Hopkins Hosp.* **17**:254-258, 1906.

2. Jones, E. M.: Phlegmonous Enteritis, *Minnesota Med.* **14**:956-959, 1931.

3. Dr. John Wyckoff supplied the clinical record of this case.

Significant Necropsy Observations.—Necropsy, performed five days after death, revealed absence of free fluid in the peritoneal cavity. The parietal peritoneum over the anterior wall in the left upper quadrant appeared rough and injected. The first portion of the jejunum was distended. About 50 cm. from the pylorus, and extending distally for 20 cm. without any sharp line of demarcation, the intestine had the character of a rigid, thickened tube. The serosa was deep red and presented several yellowish areas, from 2 to 10 mm. in diameter, from which purulent material could be expressed. A fibrinopurulent exudate was deposited on this portion of the intestine, as well as between coils of intestine in the lower part of the abdomen. The mesentery contiguous with the involved intestine was similarly indurated and presented small foci of suppuration. On section, the affected region of the jejunum showed marked thickening of the submucosal coat. The transverse plicae appeared as markedly swollen and rigid folds without visible evidence of ulceration. The submucosa varied from 5 to 10 mm. in thickness and was uniformly gray (figs. 1 and 2).

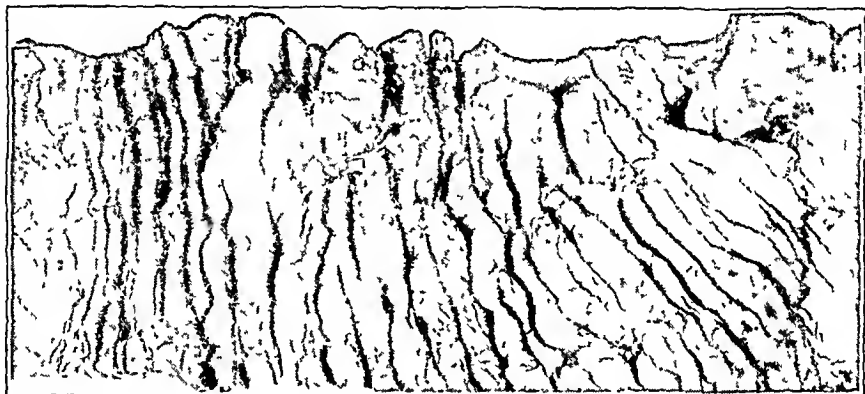


Fig. 1 (case 1).—View of the opened jejunum. Note the markedly swollen plicae circulares, the absence of ulceration of the mucous membrane and the transition from the involved to the uninvolved portions of the intestine. A block has been removed for microscopic study.

Microscopic examination of the involved portion of the jejunum revealed marked diffuse edema, fibrinous exudation and dense polymorphonuclear leukocytic infiltration of the submucosa. The mucous membrane formed a continuous lining, although it appeared to be necrotic or autolyzed. There was a focal extension of the exudate into the muscularis and serosa, where miliary abscesses were encountered. The mesentery presented similar evidence of acute suppurative inflammation. Micro-organisms could not be demonstrated in sections stained by the Gram-Weigert technic or with methylene blue.

The appendix showed atrophic and sclerotic changes. In the lungs were found small tuberculous foci in both apexes and a few scattered minute tubercles in the lower lobes, but neither cavitation nor caseation was present. There was also a small hemorrhagic pulmonary infarct in the upper lobe of the left lung. The other organs exhibited nothing of note.

Summary.—A 46 year old man, with a history of chronic alcoholism, became acutely ill with cramplike abdominal pain, vomiting and diarrhea, chills, fever

and leukocytosis. Abdominal examination revealed tenderness and inconstant rigidity of the left side of the abdomen, accompanied by an ill defined mass in the left upper quadrant and to the left of the umbilicus. Death occurred six days after the onset of symptoms. Necropsy revealed an acute diffuse fibrinopurulent inflammation of 20 cm. of the jejunum, affecting chiefly the submucosal coat, without mucosal ulceration, and extending to the serosa and into the mesentery. A localized fibrinopurulent peritonitis accompanied this extension.

CASE 2.—J. P., a 45 year old white man, was admitted to the psychiatric service of the Bellevue Hospital on April 10, 1936. He was confused and disoriented, and efforts to obtain a coherent history were unsuccessful. He appeared chronically ill but was not in acute distress. The abdomen showed distention and tympany, spasticity, which was more marked on the right side, and tenderness of the right lower quadrant. The temperature was 98 F., the pulse rate 110, the blood pressure 114 systolic and 74 diastolic and the white blood count 12,500, with 71 per cent polymorphonuclear leukocytes, 14 per cent metamyelocytes II and 15 per cent lymphocytes.

In the following forty-eight hours the patient lapsed into a semicomatose state, and bladder and rectal incontinence developed. No vomiting was observed,



Fig. 2 (case 1).—A side view of the wall of the opened jejunum, showing the marked swelling of the plicae circulares.

but numerous watery stools were passed. The abdominal signs did not change. The temperature varied between 98 and 101 F., the blood pressure dropped to 80 systolic and 60 diastolic, the urine showed a trace of albumin and the non-protein nitrogen content of the blood was 100 mg. per hundred cubic centimeters. Death occurred forty-eight hours after admission.

Significant Necropsy Observations.—Necropsy, performed six days after death, showed 500 cc. of a yellow slightly sanguineous fluid with flakes of fibrin in the peritoneal cavity. The peritoneum was dull and lusterless. There were many fresh fibrinous adhesions between loops of the small intestine. There was marked distention of the upper loops of the small intestine, diminishing gradually in the ileum. Near the termination of the ileum, for a distance of about 30 cm., the intestine was heavy and firm and appeared gray, with a thick fibrinous deposit on the serosa. On section, the distal portion of the ileum presented a thickened, firm, gray appearance, with prominent circular plicae and a soft gray submucous coat about 5 mm. in thickness. There was no apparent ulceration of the mucosa and no evidence of hemorrhage or gangrene. The process began gradually about 50 cm. above the ileocecal valve and ended abruptly about 20 cm. above the latter. The adjacent mesentery was indurated and exhibited purulent foci. The branches of the mesenteric artery at the attachment of the intestine were plugged by soft grayish red thrombotic masses, which extended proximally up to the point of bifurcation of a branch of the second order. The latter, as well as the larger

branches and the trunk of the superior mesenteric artery, exhibited a smooth intima. The mesenteric and portal veins were natural.

Microscopic examination of the involved section of ileum revealed marked thickening of the wall due, chiefly, to edema, fibrinous exudation and dense infiltration by polymorphonuclear leukocytes in the submucosal layer (fig. 3). The mucous membrane, although exhibiting focal acute inflammatory and necrotic changes, was not ulcerated. The muscular layers presented well preserved muscle bundles, between which were many polymorphonuclear leukocytes. The serosa in some sections appeared intact and in others showed a dense exudate of polymorphonuclear leukocytes and fibrin. Bacilli and cocci, the latter in short chains and diplococcus forms, were demonstrated on the mucous membrane and in the submucosa by the Gram-Weigert technic.

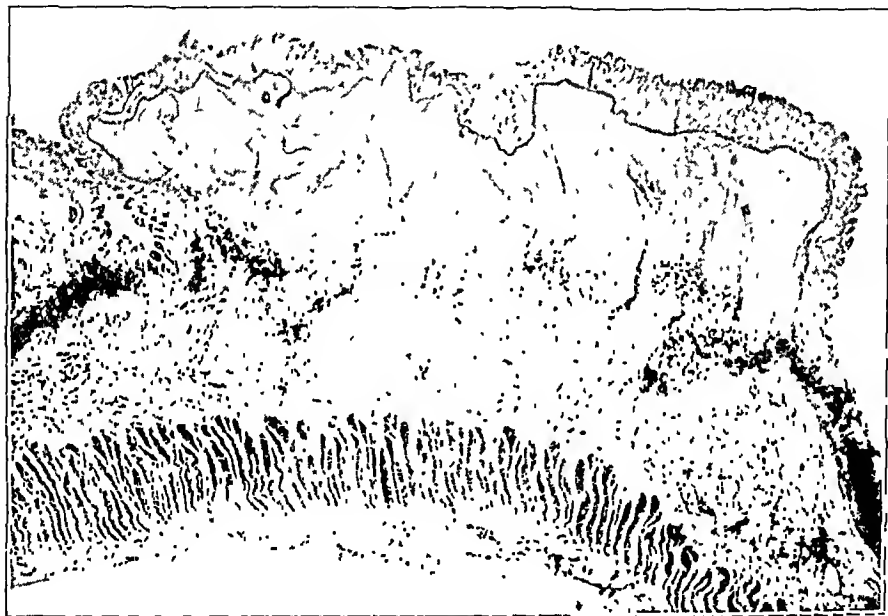


Fig. 3 (case 2).—View of a section of the ileum showing the marked thickening of the submucosal coat with edema, fibrin formation and infiltration by polymorphonuclear leukocytes. The mucous membrane forms a continuous lining. Hematoxylin and eosin stain.

There was dense infiltration of the mesentery by polymorphonuclear leukocytes, and the mesenteric lymph nodes presented evidence of acute inflammation.

Some of the small arteries in the tunica propria and submucosa showed infiltration of their walls by polymorphonuclear leukocytes and were plugged by homogeneous eosinophilic masses. The thrombosed branches of the superior mesenteric artery appeared in sections to be filled by recent thrombi composed largely of red cells and fibrin. There were no inflammatory or arteriosclerotic changes in these vessels, although there was a diffuse suppurative inflammation of the mesentery through which these vessels coursed. A few small venous channels were also plugged by recent thrombi. In one of the sections through the mesentery an artery was found, about 1 mm. in diameter, containing an organized and canalized thrombus.

In the appendix were found atrophy of the lymphoid elements and a diffuse increase in the fibrous tissue of the submucosa. Plasma cells and eosinophilic polymorphonuclear leukocytes were present in moderate number throughout the mucous membrane.

The liver presented fatty change, and there were congestion and edema of the lungs.

Summary.—A 45 year old white man, from whom a coherent history was not obtainable, died forty-eight hours after admission to the hospital with the clinical picture of mental confusion and disorientation, abdominal distention, spasticity and tenderness of the right lower abdominal quadrant, leukocytosis and shock. Necropsy revealed acute diffuse fibrinopurulent inflammation of about 30 cm. of ileum, affecting chiefly the submucosal coat and extending to the serosa and into the mesentery. The mucous membrane was not ulcerated. There was terminal thrombosis of some of the branches of the mesenteric vessels in the involved intestine and mesentery; in one section through the mesentery a small artery was found containing a completely organized and canalized thrombus.

REVIEW OF THE LITERATURE

Acute phlegmonous enteritis was mentioned by Rokitansky⁴ in 1842 and called "enteritis submucosa suppurativa." Bohmansson,⁵ who summarized the literature in 1923, accepted as cases of acute phlegmonous enteritis those in which an "acute, purulent inflammatory process in the submucosa and subserosa of the intestine" was reported. The cases recorded in the literature as instances of "phlegmonous enteritis" or *Darmphlegmone*, and which we have selected for the review of the pathologic and clinical features of this disease, represent instances of an apparently primary suppurative lesion of the intestinal wall, affecting chiefly the submucosal coat. Localized suppurative lesions of the intestine secondary to ulcer or carcinoma are not considered. The relationship of this lesion to a similar or identical process in the stomach and large intestine and to regional subacute and chronic nonspecific inflammatory lesions of the intestine will be considered.

Distribution of the Lesion.—Of forty-one reported cases, the lesion in twelve was localized to the duodenum or the duodenum and the proximal portions of the jejunum,⁶ in twenty-two the jejunum alone was involved⁷ and in seven the lesion was limited to the ileum.⁸

4. Rokitansky, C.: *Lehrbuch der pathologischen Anatomie*, Vienna, Wilhelm Braumüller, 1842.

5. Bohmansson, G.: *Acute Purulent Processes in the Intestinal Wall*, *Acta chir. Scandinav.* 55:437-489, 1922-1923.

6. (a) Askanazy, M.: *Ueber Enteritis phlegmonosa*, *Centralbl. f. allg. Path. u. path. Anat.* 6:313-319, 1895. (b) Deutmoser, cited by MacCallum.¹ (c) Ungermann, E.: *Duodenitis phlegmonosa*, *Virchows Arch. f. path. Anat.* 193: 445-455, 1908. (d) Neupert: *Demonstration eines Präparates von Enteritis phlegmonosa*, *Zentralbl. f. Chir.* 37:713, 1910. (e) Taylor, G., and Lakin, C.: *A Fatal Case of Phlegmonous Inflammation of the Duodenum Fol-*

Age and Sex.—The distribution of patients in the various decades is as follows: first decade, one; second decade, none; third decade, three; fourth decade, seven; fifth decade, four; sixth decade, twelve; seventh decade, nine; eighth decade, two; ninth decade, one. Thirty of the cases were in males and nine in females. In two cases the age and sex of the patient were not given.

Etiology and Pathogenesis.—The bacteriologic picture as well as the histopathologic features suggest that the lesion is due to invasion of the wall of the intestine by pyogenic micro-organisms. In a few instances cultures have been made of the pus in the intestinal wall. The micro-organisms obtained have been "Streptococcus,"⁹ Staphylococcus,⁵ Pneumococcus,^{7h} Bacillus coli^{6e} and Staphylococcus and "Streptococcus" together.^{6a} More commonly, micro-organisms have been demonstrated in sections of the tissue or in direct smears of the pus, and in most instances the presence of "streptococci" or gram-positive cocci in short chains or diplococcus forms is recorded.¹⁰ In a few instances the presence of micro-organisms could not be verified in sections.¹¹

following Impaction of a Fish Bone, *Lancet* 2:224-225, 1911. (f) Black, K.: Two Cases of Phlegmonous Duodenitis, *Practitioner* 95:104-107, 1915. (g) Frising, G., and Sjövall, E.: Die phlegmonöse Enteritis in Duodenum und Anfangsteil des Jejunums, *Beitr. z. klin. Chir.* 83:1-25, 1913. (h) Hellström, N.: Zur Kenntnis der primären Phlegmone im Darm, *ibid.* 115:602-628, 1919. Bohmansson.⁵

7. (a) Bellfrage and Hedenius. (b) Moissejew; Hoffman, and Neupert, cited by MacCallum.¹ (c) Müller, W.: Ein Beitrag zur Pathologie der Dünndarmphlegmonen, *Virchows Arch. f. path. Anat.* 216:416-423, 1914. (d) von Saar, G. F.: Zur Kenntnis der phlegmonösen Prozesse des Darmkanals, *Arch. f. klin. Chir.* 106:228-234, 1915. (e) Holmdahl, D. E.: Beitrag zur Kenntnis der eitrigen, ulcerösen, und diphtheritischen Prozesse im Dünndarm, *Beitr. z. klin. Chir.* 99:193-227, 1916. (f) Zoepffel, H.: Heilung der Enteritis phlegmonosa durch Darmresektion, *Deutsche Ztschr. f. Chir.* 154:266-270, 1920. (g) Wilson, J. B. F.: Acute Primary Phlegmonous Enteritis, *Lancet* 1:1244, 1922. (h) Leuchtenberger, R.: Zur Kasuistik der Darmphlegmone, *Virchows Arch. f. path. Anat.* 246:418-425, 1923. (i) Bundschuh, E., and Wolff, E. P.: Zur Kenntnis der Darmphlegmone, *Arch. f. klin. Chir.* 136:438-448, 1925. (j) Krüger, H.: Ueber Ileus durch Dünndarmphlegmone, *ibid.* 153:813-815, 1928. (k) Irwin, C. G., and McDonald, S.: Two Cases of Localized Phlegmonous Enteritis, *Brit. J. Surg.* 19:362-373, 1932. MacCallum.¹ Bohmansson.⁵ Neupert.^{6d} Hellström.^{6h}

8. (a) Glaus, A.: Ueber primäre Enteritis phlegmonosa staphylococcica ilei, *Berl. klin. Wchnschr.* 55:474-477, 1918. (b) Fromme: Berichte aus den Chirurgischen Gesellschaften, *Zentralbl. f. Chir.* 51:2386, 1924. (c) Metge, E.: Beitrag zur Kenntnis der primären Darmphlegmone, *ibid.* 52:2474-2475, 1925. (d) Neugebauer, F.: Phlegmone des Ileums, *Beitr. z. klin. Chir.* 144:228-230, 1928. (e) Nash, F. W. B.: Acute Localized Phlegmonous Enteritis Complicating Pregnancy, *Brit. M. J.* 2:792-793, 1932. Jones.² Bohmansson.⁵

9. Hellström.^{6h} Bundschuh and Wolff.⁷ⁱ

10. MacCallum.¹ Bohmansson.⁵ Ungermann.^{6c} Neupert.^{6d} Frising and Sjövall.^{6g} Hellström.^{6h} Moissejew, cited by MacCallum.¹ Müller.^{7c} Irwin and McDonald.^{7k} Neugebauer.^{8d}

11. Hellström.^{6h} Zoepffel.^{7f}

Although the infection is frequently assumed to be of enterogenous origin, few reports offer a convincing demonstration of the portal of entry. Changes in the mucous membrane are not constantly present, and the character of the mucous membrane lesion suggests that it is secondary to the process in the submucosa. Various suggestions have been presented concerning the influence responsible for the penetration of organisms from the lumen into the wall of the intestine. In the case reported by Askanazy^{6a} the onset of symptoms was preceded several days before by abdominal trauma, which was interpreted as the inciting cause, although no visible defect was demonstrated in the mucous membrane of the involved jejunum. In MacCallum's¹ case, too, abdominal trauma occurred several days preceding the onset of symptoms. In a case reported by Ungermann^{6c} duodenal diverticuli containing sharp bony spicules were found in the phlegmonous lesion, and in another case (Taylor and Lakin^{6e}) impaction of a fish bone was demonstrated in the wall of the involved duodenum. Part of a fish bone was found in the duodenal contents in a case reported by Frising and Sjövall.^{6f} Intestinal parasites (*Oxyuris*) have been reported in one instance (Fromme^{6b}). In four cases the phlegmonous intestinal lesion complicated atrophic cirrhosis of the liver,¹² and Leuchtenberger^{7b} suggested that "intestinal catarrh" due to portal stasis may play a predisposing rôle. In two instances the disease complicated pregnancy.¹³

There is no convincing evidence that the infection is ever of hematogenous nature. The lesion has occurred as a complication of pneumococcic pneumonia in two instances,¹⁴ of scarlet fever in one instance² and of acute tonsillitis in another;⁵ but an enterogenous source of pyogenic organisms cannot be excluded in these instances.

Further support for the belief in the enterogenous nature of the infection is to be gained by consideration of the comparative frequency of the phlegmonous lesion in different parts of the gastro-intestinal tract. In the stomach as well as in the colon there occurs an acute phlegmonous lesion which is closely similar in its histopathologic and bacteriologic features and clinical course to the acute phlegmonous lesion of the small intestine. However, acute phlegmonous gastritis apparently occurs much more frequently than the analogous lesion in the intestine. Szabó¹⁵ in 1934 stated that there were two hundred and fifty-three cases of gastric phlegmon reported in the literature. Acute

12. Matthes, cited by MacCallum.¹ Neupert.^{6d} Leuchtenberger.^{7b} Bundschuh and Wolff.⁷¹

13. Bohmansson.⁵ Neugebauer.^{8d}

14. Wilson.^{7g} Leuchtenberger.^{7b}

15. Szabó, K.: Einiges über Magen und Darmphlegmonen, mit Rücksicht auf zwei Dickdarmphlegmonenfälle, *Zentralbl. f. Chir.* 61:947-952, 1934.

phlegmon of the colon occurs much less commonly. Of thirteen proved cases reported in the literature, the lesion in six was limited to the cecum,¹⁶ in four to the cecum and ascending colon,¹⁷ in one to the transverse colon,¹⁸ in one to the descending colon¹⁹ and in one to the sigmoid colon.^{6h}

The greater predilection of the lesion for the stomach and the upper portion of the small intestine and the diminishing incidence of the lesion in the distal portion of the gastro-intestinal canal suggest that the causative organisms are swallowed. It has been emphasized that chronic gastritis is a frequent finding in acute phlegmonous gastritis, and it has been suggested that the former lesion predisposes to the latter by lowering or abolishing the acidity and bactericidal power of the gastric juice.²⁰ The high incidence of chronic alcoholism in phlegmonous gastritis is interpreted as further evidence of the rôle of chronic gastritis and anacidity in the genesis of the phlegmonous lesion (Konjetzny and Schnarrwyler²¹).

A similar correlation in phlegmonous lesions of the intestine has not yet been established, although the rôle of chronic gastritis has been suggested.²² Hellström^{6h} called attention to the history of chronic alcoholism in two of Müller's cases, it was noted by Bsteh^{16a} in an instance of phlegmonous cecitis, and it was present in case 1 of this report.

16. (a) Bsteh, O.: Zur Kenntnis der Darmphlegmone, *Arch. f. klin. Chir.* **169**:193-203, 1932. (b) Teutschlaender, O., and Valentin, B.: Enteritis phlegmonosa (durch Darmresektion geheilte Caecumphlegmone), *Mitt. a. d. Grenzgeb. d. Med. u. Chir.* **38**:469-480, 1924-1925. (c) Pataky, Z.: Mit Dickdarmphlegmone komplizierter Appendicitisfall, *Zentralbl. f. Chir.* **54**:1566-1568, 1927. (d) Köntzey, E., and Jáki, J.: Ueber einen Fall von primärer Coecumphlegmone, *ibid.* **55**:1223-1226, 1928. (e) Bundschuh and Wolff.⁷ⁱ

17. Biederman, H.: Durch Darmresektion geheilte primäre Phlegmone des Dickdarms mit Inversion der Coecalwand, *Beitr. z. klin. Chir.* **124**:718-721, 1926. (b) Ingier, A.: Ein Fall von Pneumokokkenmetastase im Colon ascendens, *Centralbl. f. allg. Path. u. path. Anat.* **21**:148-156, 1910. (c) von Saar.^{7d} (d) Leuchtenberger.^{7h}

18. Goldschmidt, F.: Ein Fall von Enteritis phlegmonosa, *Arch. f. klin. Med.* **40**:400-404, 1887.

19. Dowd, C. N.: Acute Phlegmonous Inflammation of the Large Intestine, *Ann. Surg.* **56**:579-581, 1912.

20. Konjetzny, G. E.: Gastritis phlegmonosa, in Henke, F., and Lubarsch, O.: *Handbuch der speziellen pathologischen Anatomie und Histologie*, Berlin, Julius Springer, 1928, vol. 4, pt. 2.

21. Schnarrwyler, cited by Adams, J. E.: Acute Primary Phlegmonous Gastritis, *Lancet* **1**:292-296, 1910.

22. Frising and Sjövall.^{6e} Hellström.^{6h}

Pathologic Picture.—Localized fibrinous peritonitis is usually present, and in the majority of instances a turbid effusion or a generalized purulent peritonitis is also found. Occasionally a serous effusion occurs.²³ Peritonitis occurs without demonstrable perforation of the intestine and may be present within twenty-four hours of onset^{6h} or absent as late as the fifth day of the disease.^{7d}

The phlegmonous lesion involves the intestine in a uniform diffuse manner for a variable distance.²¹ Usually from 15 to 40 cm. of intestine is affected by the phlegmonous lesion, though the latter may be as limited as 4 cm.^{7e} or as extensive as 60 cm.^{7f} There is no apparent correlation between the duration of symptoms in different subjects and the length of the phlegmon. Except in the case described by Matthes,²⁵ in which the phlegmonous lesion involved the entire gastro-intestinal canal, coexistence of a gastric and intestinal phlegmon or of the latter and a phlegmon of the colon has not been described. The involved portion of the intestine is sometimes sharply demarcated from the uninvolved area, or the division may be more gradual. Proximal or distal to the phlegmon, the intestine may exhibit extensive edema.

The more characteristic features of the involved intestine are its stoutness, its heaviness and its rigidity. It may be swollen to from three to four times its normal diameter and feels indurated and inflexible. The serosa is frequently red and edematous and possesses fibrinous deposits or yellowish gray purulent foci. After the intestine is opened, the swollen and rigid character of the plicae circulares proves striking; these circular folds may measure a centimeter or more in thickness. On the cut surface of the intestinal wall may be seen the broadly thickened translucent gray submucosa. The thickening of the submucosa, and particularly of the transverse plicae, may produce stenosis of the lumen of the viscus. The mucous membrane in most instances appears gray and edematous but is otherwise intact; less often there is focal necrosis, suppuration or ulceration. Small scattered abscesses are frequently found in the submucosa and extend into the lumen or subserosa.

The contiguous mesentery is frequently edematous and sometimes involved in the phlegmonous process. In duodenal phlegmon there may be edema and infiltration, by polymorphonuclear leukocytes, of the retro-duodenal tissue and the pancreas.^{6g} The mesenteric lymph nodes are enlarged and occasionally suppurative. Large abscesses of the mesentery accompanying acute phlegmonous enteritis have been noted by Müller^{7c}

23. Black.^{6f} Zoepffel.^{7d}

24. Instances of localized abscesses or inflammatory nodules in the intestinal wall are described by Bsteh^{16a} and Bohmansson.⁵

25. Matthes, cited by MacCallum.¹

and Bohmansson.⁵ Thrombosis of the regional arteries or veins, as observed in case 2, has not been recorded in the reported cases.

The microscopic picture is that of edema, fibrinous inflammation and dense diffuse infiltration by neutrophilic polymorphonuclear leukocytes, the process affecting chiefly the submucosa. The mucous membrane may appear normal or show edema, acute inflammation or necrosis. In the case reported by Metge^{8c} the inflammatory cells were chiefly eosinophilic polymorphonuclear leukocytes.

Symptoms and Signs.—In most instances the disease is characterized by the sudden onset of intense abdominal pain, which is epigastric or periumbilical in nature. Frequently the pain is colicky. Vomiting constantly follows and may become fecal. Often a chill occurs early in the disease.²⁶ Obstipation is commonly observed, although diarrhea occasionally occurs. Blood may rarely appear in the stool.^{7f} Jaundice occurred in a few instances in which the first part of the duodenum was involved.²⁷

The patient generally appears acutely and critically ill. The abdomen is frequently distended, and tenderness is present in the epigastrium, periumbilical region or right lower quadrant. Rigidity is absent as frequently as it is present. In a few instances, as in case 1, an ill defined mass may be palpated.

Fever and leukocytosis are present in most cases, the former ranging from 100 to 104 F. However, the temperature is not infrequently normal.²⁸

Prognosis and Treatment.—In the cases analyzed in this report thirty-four of the patients died within from thirty hours to a week after the onset of symptoms. In one case the course was more prolonged, death occurring on the fortieth day.^{6b} In no instance has a correct pre-operative diagnosis been made; the patients have come to operation most frequently with the diagnosis of acute appendicitis or intestinal obstruction. Twenty-two died without surgical intervention. Laparotomy was done in thirteen cases in which death occurred, resection being performed in three and enterostomy, gastro-enterostomy or drainage in ten.

In seven cases recovery occurred after resection of the involved intestine. Of the cases in which recovery followed resection, in five the condition was acute phlegmonous ileitis,²⁹ and in two, acute phleg-

26. Black.^{6f} Frising and Sjövall.^{6g} Hellström.^{6h} Bellfrage and Hedenius.^{7a} Irwin and McDonald.^{7k}

27. Deutelmöser, cited by MacCallum.¹ Ungermann.^{6c} Frising and Sjövall.^{6g} Holmdahl.^{7e}

28. Frising and Sjövall.^{6g} Zoepffel.^{7f} Kruger.^{7j}

29. Bohmansson.⁵ Fromme.^{5b} Metge.^{8c} Neugebauer.^{9d} Nash.^{8e}

monous jejunitis.³⁰ The length of the involved intestine in these cases varied from 8 to 50 cm. It is noteworthy that in the seven instances in which the involvement was limited to the ileum, five of the patients recovered, whereas only two of the twenty-three patients with acute phlegmonous jejunitis recovered. This is at least partly due to the difficulties of performing a resection when the proximal portion of the jejunum is involved. In this connection it is to be noted that six of thirteen patients with acute phlegmonous colitis recovered after resection of the involved intestine.³¹

Whether recovery can occur without resection is impossible to affirm, for in the absence of a resected specimen a convincing diagnosis is not possible. Several reports exist in which the findings at operation suggested the presence of a phlegmon of the intestine, and recovery occurred without resection.³² Most convincing is the case described by Wilson,^{7c} in which recovery followed a lateral anastomosis above and below the affected portion of the jejunum.

Relationship of Acute Phlegmonous Enteritis to Chronic Nonspecific Inflammatory Lesions of the Intestines.—Recently, many reports have appeared of chronic nonspecific inflammatory lesions involving the small or large intestine, to which various designations have been assigned, namely: inflammatory tumor,³³ chronic interstitial enteritis,³⁴ nonspecific granuloma of the intestine,³⁵ regional ileitis,³⁶ nonspecific granuloma of the gastro-intestinal tract,³⁷ chronic cicatrizing enteritis³⁸ and regional enteritis.³⁹

The etiology of this lesion in most cases is obscure. It is possible that in some instances an acute localized phlegmonous process due to pyogenic cocci may form a chronic nonspecific productive inflammatory

30. Bohmansson.⁵ Krüger.^{7j}

31. von Saar.^{7d} Brundschuh and Wolff.⁷ⁱ Teutschlaender and Valentin.^{16b} Pataky.^{16c} Biederman.^{17a} Dowd.¹⁹

32. Jones.² Bohmansson.⁵

33. Braun, H.: Ueber entzündliche Geschwulste am Darm, Deutsche Ztschr. f. Chir. **100**:1-12, 1909.

34. Dalziel, T. K.: Chronic Interstitial Enteritis, Brit. M. J. **2**:1068-1069, 1913.

35. Moschcowitz, E., and Wilensky, A. O.: Nonspecific Granulomata of Intestine, Am. J. M. Sc. **166**:48-66, 1923.

36. (a) Crohn, B. B.; Ginzburg, L., and Oppenheimer, G. D.: Regional Ileitis, J. A. M. A. **99**:1323-1329 (Oct. 15) 1932. (b) Koster, H.; Kasman, L. P., and Scheinfeld, W.: Regional Ileitis, Arch. Surg. **32**:789-809 (May) 1936.

37. Erdmann, J. F., and Burt, C. V.: Nonspecific Granuloma of Gastro-Intestinal Tract, Surg., Gynec. & Obst. **57**:71-80, 1933.

38. Donchess, J. C., and Warren, S.: Chronic Cicatrizing Enteritis with Involvement of Cecum and Colon, Arch. Path. **18**:22-29 (July) 1934.

39. Brown, P. W.; Bargaen, J. A., and Weber, H. M.: Regional Enteritis, Proc. Staff Meet., Mayo Clin. **9**:331, 1934. Meyer, K. A., and Rosi, P. A.: Regional Enteritis (Non-Specific), Surg., Gynec. & Obst. **62**:977-988, 1936.

lesion. In the literature many cases of a similar chronic intestinal lesion are recorded under the term *Darmphlegmone*,⁴⁰ and several authors have presented cases which were interpreted as representing transitional stages between an acute and a subacute or chronic phlegmonous process due to pyogenic cocci.⁴¹ In the stomach, too, lesions have been observed which suggested that acute phlegmonous gastritis caused by pyogenic cocci may pass into a subacute or chronic stage (Konjetzny²⁰).

The following case, observed at Bellevue Hospital, illustrates one in which the lesion may represent a transitional stage between the acute phlegmonous and the chronic nonspecific regional type.

CASE 3.—J. K., a 34 year old woman, was admitted to the third surgical division of the Bellevue Hospital in September 1923. Pain in the right lower abdominal quadrant appeared a week before her admission and was followed by nausea and feverishness. Abdominal examination revealed moderate rigidity and marked tenderness in the right lower quadrant. The temperature was 100.5 F.; the white blood count was 8,900 with 91 per cent neutrophilic polymorphonuclear leukocytes.

At operation, performed the day of the patient's admission, the terminal 21 cm. of ileum and cecum was found to be thickened and rigid. The appendix appeared to be normal. The involved portion of the ileum and the cecum were resected, and a lateral anastomosis performed. After two weeks of slight purulent discharge, the wound closed, and the patient made an apparent recovery.

She remained free from symptoms, until August 1929, at which time she reentered the hospital because of abdominal discomfort and fever. She was febrile for about four weeks, during which time she received several transfusions of blood, and gradually the abdominal pain and fever subsided. A similar episode occurred again in February 1930. In August 1932 she again entered the hospital with an abscess of the lower anterior abdominal wall. After incision and drainage of the abscess, multiple fecal fistulas appeared. Ileosigmoidostomy was performed in January 1933, but the fistulas have not yet entirely closed.

The resected specimen presented for examination about 20 cm. of the lower part of the ileum together with the cecum and appendix. The wall of the intestine was thickened, and the mucosa was injected. The mesentery contained a small abscess cavity.

Microscopic sections revealed diffuse thickening of the wall of the intestine, chiefly of the submucosal coat. The mucosa exhibited focal superficial ulceration and dense infiltration by neutrophilic polymorphonuclear leukocytes, lymphocytes and plasma cells. The submucosa, muscularis and serosa showed diffuse infiltration by abundant eosinophilic and neutrophilic polymorphonuclear leukocytes, plasma

40. (a) Sauer, H.: Streptokokkenphlegmone des Colon ascendens im Anschluss an eine durch Trichocephalus entstandene entzündliche Dickdarmgeschwulst, Deutsche Ztschr. f. Chir. **180**:27-36, 1923. (b) Fischer, A.: Ueber Phlegmone der Darmwand, Zentralbl. f. Chir. **58**:1243-1247, 1931. (c) Fossel, M.: Ueber einen Fall von operativ geheilter Darmphlegmone, *ibid.* **59**:1160-1165, 1932. (d) Ostrowski, S.: Zur Klinik der Dünndarmphlegmone. Rezidiv 4 Monate nach erfolgreicher Primärresektion, *ibid.* **60**:501-509, 1933. (e) Peters, K. O.: Drei weitere Fälle von Darmphlegmone im Ileum, *ibid.* **61**:1208-1216, 1934. (f) Konjetzny, G. E.: Phlegmone des Dün- und Dickdarms auf der Grundlage einer einfachen Enteritis bzw. Colitis erosiva, *ibid.* **62**:978-987, 1935. (g) Teutschlaender and Valentin.^{16b}

41. Teutschlaender and Valentin.^{16b} Sauer.^{40a} Ostrowski.^{40d} Konjetzny.^{40f}

cells, lymphocytes and fibroblasts. In the cecum there was considerable increase in the subserosal tissue, with numerous young histiocytes and fibroblasts. The abscess in the mesentery was filled with polymorphonuclear leukocytes and was surrounded by a wall of granulation tissue.

Although it must be admitted that the anatomic characteristics of certain specimens suggest a close relationship between the acute phlegmonous and the chronic forms, there is no convincing evidence that they are of identical etiology. It is noteworthy that in the small intestine the majority of acute phlegmonous lesions occurred in the duodenum or jejunum (thirty-four of forty-one), whereas the majority of chronic lesions were limited to the terminal portion of the ileum (sixty-five of eighty^{36b}). Similarly, reports of chronic regional nonspecific inflammatory lesions of the colon appear in the literature much more frequently than do reports of acute phlegmonous colitis.^{36b} Whether this points to a different etiology of the acute phlegmonous and chronic lesions or is a reflection of a variation in the course of the disease in different portions of the gastro-intestinal canal cannot be determined.

SUMMARY

Two fatal cases of acute phlegmonous enteritis are reported, in one the condition being limited to the jejunum and in the other to the ileum.

The pathologic and clinical characteristics in forty-one similar cases reports of which were gathered from the literature are reviewed. It appears that acute phlegmonous enteritis is a well defined clinical and pathologic entity, and although it is most likely an infection of the wall of the intestine with pyogenic micro-organisms of enterogenous origin, a portal of entry is only rarely demonstrated.

The possible relationship of the acute phlegmonous lesion of the intestine to chronic nonspecific inflammatory lesions of the intestine is discussed, and a case is presented which suggests a transitional stage between the two.

SCLEROSING SARCOMA OF BONE

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BALTIMORE

In the older literature, both pathologic and surgical, sarcomas of bone were usually divided into the central and the periosteal type. The central type was frequently referred to as telangiectatic because of its hemorrhagic appearance on macroscopic examination and the absence of any clearly defined picture on microscopic examination. Tumors which are now referred to as osteolytic sarcoma, small round cell sarcoma of bone (Ewing's tumor) and central chondrosarcoma were also considered to be of this type. According to the older classification, periosteal sarcoma likewise had no well defined histologic characteristics. The fibrocellular forms, now recognized as either fascial sarcoma, or sarcoma arising from the nerve sheath and secondarily involving bone, and chondrosarcoma, which in the early stage is mostly subperiosteal and outside of the cortical bone, were classified under the periosteal type. Sclerosing sarcoma, which develops from the periosteum and cortical bone, usually at the ends of the long bones, was also included in this classification.

Bloodgood¹ in 1923 made the following statement concerning the roentgenographic picture in a case referred to him:

I can also see a somewhat wedge-shaped area occupying the inner head of the tibia, its base towards the periosteal growth in which the normal architecture of the cancellous bone is blurred by a cloudy defect. This means that there is either a periosteal growth of tissue, or an infiltration in the cancellous bone. In my experience this x-ray picture is more often seen in sclerosing sarcoma than in any inflammatory lesion and until recently we never had an opportunity to observe an early picture such as this.

A number of radiologists and surgeons saw this picture, and apparently the opinion of all favored a diagnosis of a low grade of osteomyelitis or tuberculosis. I have before me the typewritten copy of a number of examinations and interpretations of this case. Every examination was negative, except for this change in the x-ray, and the palpation of the soft, tender swelling, as noted above.

The lateral views, made November 1st, show no evidence of periosteal bone formation, but only the slight cloudy defect of the upper end of the tibia.

In a discussion of this case Bloodgood stated:

My studies agree with Ewing that this is a distinct type, and I propose in a second communication to make a careful study with illustrations of this type of

From the Laboratory of Surgical Pathology of the Johns Hopkins Hospital.

1. Bloodgood, Joseph Colt: J. Radiol. 4:46 (Feb.) 1923.

sarcoma. . . . My studies so far seem to be convincing that the sclerosing type of sarcoma of bone should be recognized in the x-ray. Its treatment will depend upon the point of view of the one responsible, the choice being between x-ray and radium radiation, and exploration, with further diagnosis by gross and frozen section, followed by resection or amputation.

DIAGNOSIS

The sclerosing sarcoma of bone on microscopic examination is found to be composed of large amounts of osseous and osteoid tissue which originate in the tumor. Such a tumor presents distinctive clinical characteristics. A sarcoma of this type may develop in any of the bones of the skeleton, but it develops relatively rarely in any but the long bones. The series reported here consists of 158 cases. In 4 the tumor developed in the skull, in 10 in the upper and lower jaws, in 3 in the vertebrae, in 4 in the bones of the pelvis and in 4 in the scapula. Not a tumor developed in the bones of the hands or feet. Of the long bones, the femur and the tibia are most frequently affected, and the lower end of the femur and the upper end of the tibia most often are the seat of tumor formation. Seventy-two of these tumors, approximately one half, occurred in the lower end of the femur or the upper end of the tibia.

Sclerosing sarcoma of bone develops most frequently in adolescents and in young adults. In 68 cases the tumor developed in patients who were from 15 to 24 years of age; in 28, in those from 14 to 15. Fourteen of the patients were from 25 to 34 years of age, and but 12 were over 35. Adults are more frequently affected when the tumor develops in the bones of the skull and in the jaws.

The tumor runs a relatively acute course, the duration of symptoms rarely being more than six months. Pain, swelling and impairment of function appear in this sequence. In approximately one half of the cases trauma was mentioned in connection with the beginning of the tumor. Pathologic fracture is rare and occurred in but 7 of the cases being reported. Fever and leukocytosis are less frequently noted than in Ewing's sarcoma. In cases in which fever was reported the temperature did not exceed 101 F., and the leukocyte count was usually under 18,000. These findings, which at times simulate those of osteomyelitis, are observed more frequently in children than in young adults. Nothing of especial significance is revealed by physical examination in the early stage. Cutaneous changes are found only in the advanced stages. Occasionally on palpation crepitus may be made out. It is caused by displacement by pressure of the spicules which radiate from the periosteum. The swelling is usually firm, continuous with the bone and smooth and elliptic.

The final diagnosis is based on the roentgen and the microscopic picture. In the long bones the tumor develops in the end of the bone on the shaft side of the epiphysial line. The most common sites for development are the lower end of the femur and the upper end of the tibia. Some degree of periosteal reaction is usually found, but the earliest evidence of tumor formation is sclerosis, which obliterates the normal markings of the bone in the part involved. The increased density shown by the roentgenogram differs from that found in Ewing's tumor and in Garré's sclerosing osteomyelitis. In the early stages of the sclerosing sarcoma a triangle of bone at one side of the metaphysis is affected, and the most marked involvement of the cancellous bone is found immediately adjacent to the epiphysial line. Rarely does such a tumor extend down the shaft any distance. The earliest indication of tumor formation on the part of the periosteum are spicules of bone laid down at right angles to the shaft. In Ewing's sarcoma the middle of the shaft of the bone is primarily affected as a rule, and the tumor usually extends along the shaft for half of its length. An anteroposterior roentgenogram reveals symmetrical involvement, the periosteum is raised and split longitudinally and radiating spicules of bone are not seen. Osseous destruction is found in the cortical and medullary parts of the bone in the early stages of Ewing's tumor but occurs in the late stages of sclerosing sarcoma. Even in sarcoma in the advanced stage sclerosis is more pronounced than osteolysis.

In Garré's sclerosing osteomyelitis, as in Ewing's tumor, the middle of the shaft is the part usually affected. The bone is symmetrically enlarged by new bone, the cortex becomes widened and the marrow cavity is obscured. This inflammatory lesion of bone may cause an "onion peel" appearance, such as is seen in Ewing's tumor, but the radiating spicules, such as those seen in sclerosing sarcoma, are usually wanting. There is generally no evidence of osseous destruction.

In the cases of sclerosing osteogenic sarcoma in the advanced stage, the "sunburst" appearance is usually seen in the roentgenogram, and above and below the region of maximum periosteal tumor formation the periosteum is raised in a characteristic manner—so-called lipping. These roentgenographic findings are the ones usually emphasized as being significant in a diagnostic sense. In the majority of cases these are not so instructive as an earlier change—evidence of sclerosis due to the formation of dense new bone which obliterates the normal markings.

The records of the cases studied in the present series reveal that sclerosing osteogenic sarcoma is frequently not diagnosed in the early stages. Two major factors contribute to these diagnostic failures. First, there is a tendency to attribute the symptoms to bursitis, neuritis

or some allied condition, and no roentgenograms are taken. Second, roentgenograms are made, but the early clouding or sclerosis in the end of the bone is either not seen, or its diagnostic significance is not recognized. The following cases are illustrative.

CASE 1.—A Negro boy aged 16 first noted pains in the right knee eight months before being examined. At first these were thought to be caused by bursitis. The pains were described as cramplike, coming on after exercise. The patient walked with a limp. Two months prior to admission to the hospital he noted a swelling along the inner portion of the leg corresponding to the region of the tibial tuberosity. The swelling grew rapidly until it reached the size of a grapefruit at the time of the patient's admission to the hospital. Examination of the region of the right knee showed a large swelling just below the knee joint which limited extension



Fig. 1 (case 1).—Roentgenogram showing sclerosis in the upper end of the tibia extending to the epiphysial line and occupying the entire breadth of the marrow cavity. The tumor extends periosteally on the medial side.

and flexion of the leg. The mass was firm and attached to bone and had several fluctuating areas. No roentgenograms had been taken. Those made after eight months of symptoms showed sclerosis and clouding of the marrow cavity in the upper third of the tibia extending to the epiphysial line (fig. 1). Radiating spicules of new bone were seen in the metaphysial region along the inner margin. Scattered areas of osseous destruction eroded the cortex and produced a mottling effect below the region of periosteal reaction. On Jan. 24, 1930, a specimen was taken from the tibia for biopsy. It disclosed numerous spindle cells and malignant osteoblasts surrounding spicules of new bone. There were occasional small giant cells. The diagnosis was osteogenic sarcoma, and an amputation through the femur at the junction of its middle and lower thirds was made on February 8.

The specimen taken from the amputated leg showed irregular areas of density in the marrow cavity toward the epiphysial line and toward the middle third of the tibia. Between these regions the bone showed necrotic tumor tissue mingled with blood occupying regions of osseous destruction. The patient died June 23, with metastasis to the lungs.

CASE 2.—A white boy aged 15 was struck by a tennis racket four months prior to examination, and since that time a rather painful, fairly large tumor, about the size of half of a small orange, had developed in the region of the left knee joint. Later consolidation of one lung developed, and thoracentesis showed a small amount of bloody fluid. Prior to the recognition of the pulmonary involvement, no roentgenograms had been taken. The roentgenograms of the lung showed a massive region of increased density throughout the entire lower part of the lung, the extreme apex being relatively clear. The other lung was entirely

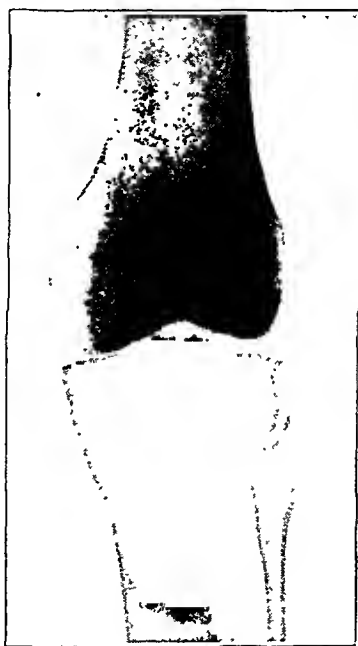


Fig. 2 (case 2).—Roentgenogram of the knee joint, showing sclerosis of the bone, the most prominent roentgenographic feature in this case. The first evidences of periosteal reaction are just beginning to be evident.

normal. Roentgenograms of the knee joint showed sclerosis of the marrow cavity at the upper end of the tibia and faintly radiating spicules of new bone in the periosteal region of the medial aspect (fig. 2).

Despite the fact that the symptoms were of only about four months' duration and the roentgenograms of the primary growth in the tibia showed little osseous destruction or extension of the tumor into the soft parts, the patient already had massive metastases to the lungs at the time of admission and died of pulmonary involvement four months later. No operation was performed.

CASE 3.—A white girl aged 15 years struck her knee with a tennis racket, and two months later pain developed, which became localized in the upper end

of the left tibia on the inner side. The first roentgenographic examination was made two months after the onset of pain (fig. 3 *A*). The picture revealed a heavy shadow (sclerosis) in the upper end of the tibia and a small defect in the cortical bone about 2 cm. below the knee joint. The lateral view revealed some increase in density, but at the time the roentgenographic appearance was considered to be normal. A plaster cast was applied. Three weeks later a second roentgenogram showed an extension of the dense shadow, so that the entire wedge of bone along the epiphysial line to a point 4 inches (10 cm.) below had dense cloudy areas. There was little periosteal reaction, and areas of increased density were interspersed among small areas of rarefaction. On Nov. 11, 1922, an exploration was made under a tourniquet; a diagnosis of sclerosing sarcoma was made on the basis of a study of frozen sections, and an amputation was performed through the lower third of the thigh (figs. 3 *B* and 4). Pain later developed in the region

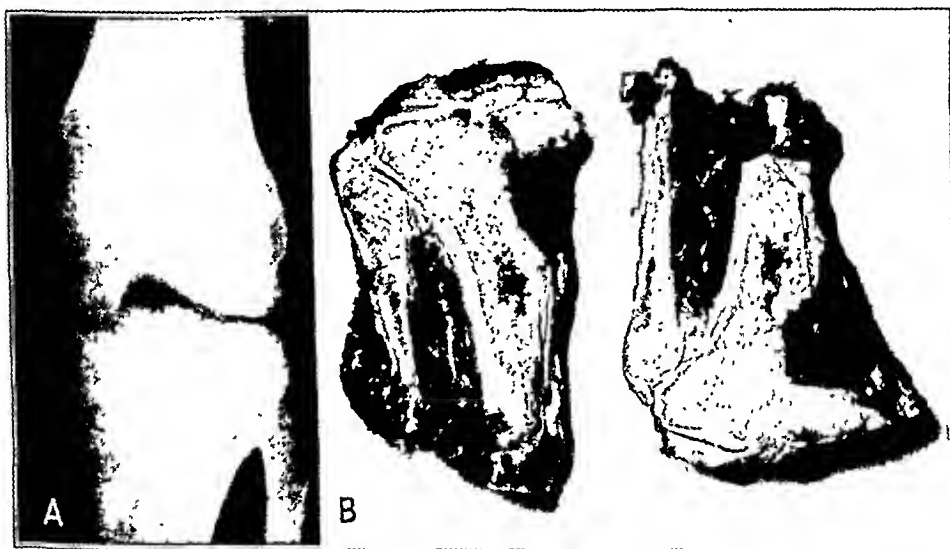


Fig. 3 (case 3).—*A*, a roentgenogram taken two months after the development of pain (the first symptom), revealing definite sclerosis in the upper end of the left tibia without any periosteal change. A biopsy was made three months after the onset of pain, and a diagnosis of sclerosing sarcoma of bone was made. An amputation was performed at the middle of the thigh. *B*, the longitudinal section of the gross specimen, showing the appearance of this type of sclerosing sarcoma.

of the spine, and fluid appeared in both sides of the chest in February 1924. The patient died of metastases in October 1924.

Variants of the sclerosing sarcoma are found in which the earliest indication of tumor formation is most marked in the subperiosteal region, and the characteristic features of a sclerosing osteogenic sarcoma are found in sections. More often, however, such a tumor contains varying amounts of cartilage and presents other transitional features, which indicates that it is related to the primary chondrosarcoma, which is in the beginning a tumor of the periosteum.

The final differentiation of sclerosing osteogenic sarcoma from other varieties of sarcoma of bone is made by microscopic examination. The former is composed of malignant osteoblasts separated by relatively large amounts of intercellular osteoid tissue. There are also found spicules of bone and spindle cells representing undifferentiated connective tissue. The irregular character of the osteoid tissue and its

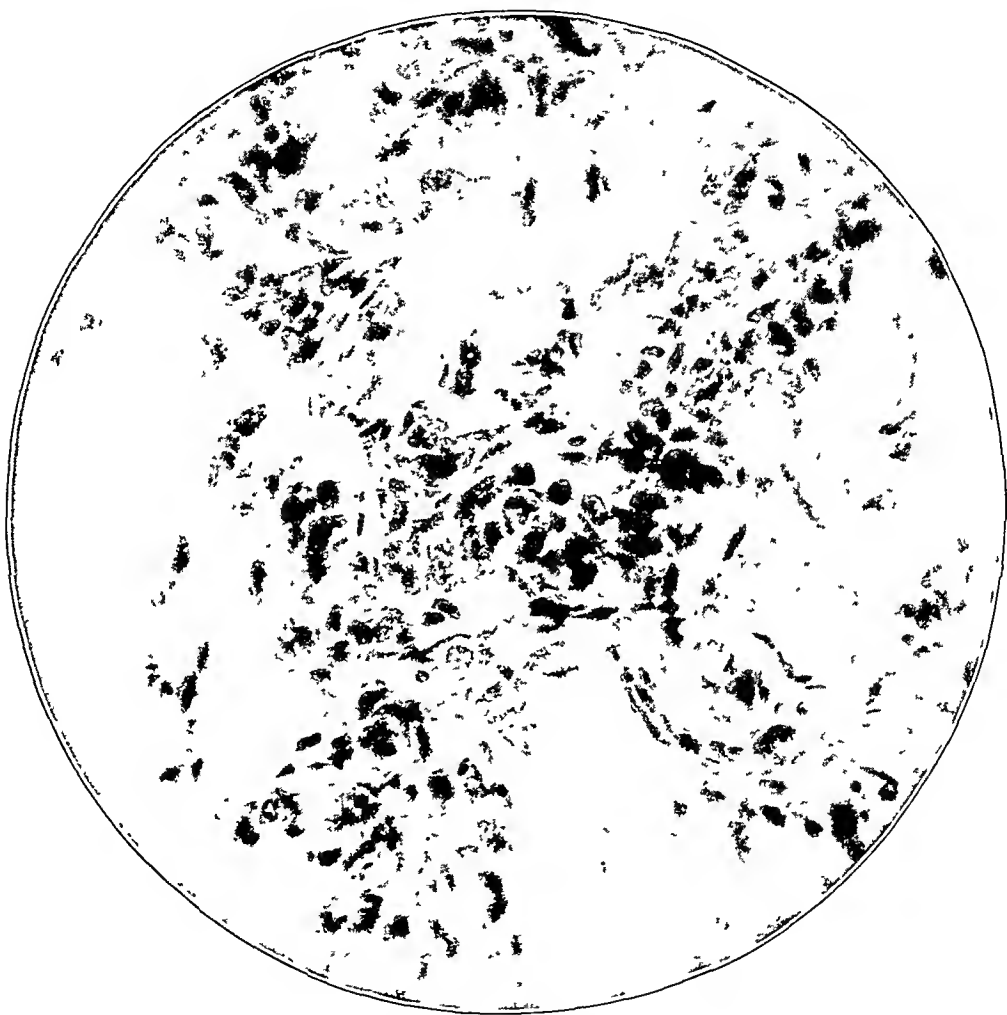


Fig. 4 (case 3).—Photomicrograph revealing the typical histologic picture of sclerosing sarcoma—malignant osteoblasts, irregular spicules of osteoid tissue and a few fibroblasts.

occurrence in all parts of the tumor in the primary growth and in metastases indicate that the osseous material is developed in the tumor (fig. 5). The tumor apparently arises from preosseous connective tissue and rapidly differentiates toward the end-product—bone.

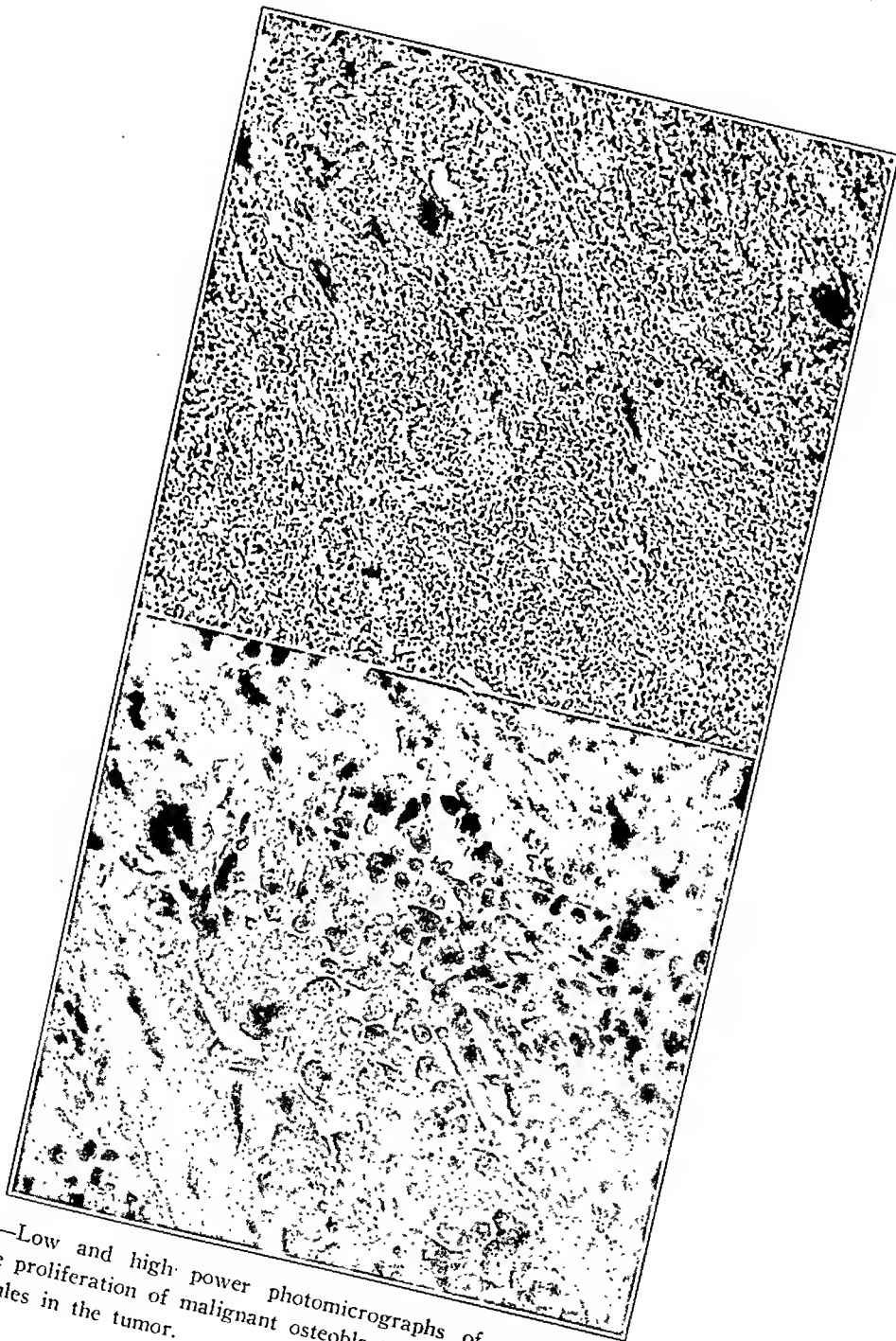


Fig. 5.—Low and high power photomicrographs of a sclerosing sarcoma, showing the proliferation of malignant osteoblasts and the formation of irregular osteoid spicules in the tumor.

PROGNOSIS

Despite the grave prognosis of sclerosing sarcoma, permanent cure is noted more frequently than in other types of sarcoma of bone. One hundred and six patients have been followed for a period of more than five years or until a fatal termination. Eighteen, or approximately 17 per cent, were living beyond the five year period, as shown in the accompanying table. Radical surgical measures were resorted to in all cases, either a resection or an amputation being performed



Fig. 6 (case 13).—Amputated specimen in a case of sclerosing sarcoma of the femur in a man aged 21. The amputation was performed by Dr. Spackman of Wilmington, Del., in April 1927. When the patient was seen in April 1937 he was entirely well. The tumor involved the entire width of the marrow cavity just above the epiphysis. There was also an extension beneath the periosteum.

(fig. 6). Resection was resorted to in the cases in which the tumor was located in the clavicle, the rib, the lower end of the humerus and the lower jaw. No cures followed irradiation. Prior to 1927, before irradiation was employed to any extent, the percentage of five year cures was nearly twice as high as in the past decade. This difference

in results is particularly striking in view of the fact that the duration of symptoms prior to treatment before 1927 averaged ten months, while during the past ten years the period averaged six months.

Data on Cases of Sclerosing Sarcoma in Which Cure Was Effected

Case	Race	Sex	Age	Location	Duration, Mo.	Symptoms	Treatment	Result
11	W	M	17	Tibia	3½	11/30/31: Amputation at middle third of thigh	Well 5 yr.
12	W	F	21	Tibia	8	Pain; swelling	April 1931: Irradiation 8/31/31: Amputation	Well 5 yr.
13	W	M	21	Femur	3½	Tumor; pain	April 1927: Amputation	Well 10 yr.
14	W	F	10	Humerus	2	Tumor; pain	7/10/25: Exploration and resection	Well 9 yr.
15	W	M	18	Femur	9	Tumor; pain	1/25/23: Amputation	Well 8 yr.
16	W	M	15	Fibula	1/5/23: Amputation	Well 5 yr. 9 mo. later
17	W	F	38	Rib (4th)	12	Pain	12/1/21: Irradiation; amputation	Well 8 yr. later
18	W	F	19	Tibia	11	Trauma; pain; tumor	7/19/21: Exploration 7/20/21: Amputation	Well 8 yr. later
19	W	F	27	Radius	48	Fracture 4 yr.; tumor 1 ½ yr.	1/2/13: Amputation	Well almost 12 yr.; lost from observation
20	W	F	6	Femur	..	Trauma; pain; tumor; pathologic fracture	1/25/21: Aspiration; radium and irradiation 5/20/21: Amputation	Well over 9 yr.
21	W	M	15	Clavicle	3	Trauma; pain; tumor	September 1920: Resection; preoperative irradiation	Well nearly 10 yr. later
22	W	F	7	Femur	2	Tumor; trauma; pain	February 1926: Exploration; amputation	Well 6 yr.; lost from observation
23	W	M	..	Femur	..	Tumor; fracture	1/18/13: Amputation	Well over 17 yr.
24	W	F	24	Femur	18	Trauma; pain; tumor	8/8/13: Amputation	Well over 16 yr.
25	W	F	11	Tibia	1½	Tumor	May 1913: Amputation	Well over 14 yr.; lost from observation
26	W	F	25	Femur	11	Trauma; pain	9/20/21: Amputation	Dead 5½ yr. later; trouble with other leg
27	W	F	19	Femur	5	Pain; tumor	August 1919: Amputation	Dead 5 yr. later; eclampsia
28	O	F	13	Mandible	9 wk.	Tenderness; loose teeth	3/9/93: Resection	Well 25 yr. later

The average duration of life rarely exceeds fifteen months in those cases in which the treatment could not be regarded as successful. The prognosis as to permanent cure becomes progressively better when the patients remain free from metastases for eighteen months after operation.

RECURRENCE

The tumor may recur in the stump when the amputation has not been performed high enough, and recurrences in the bone considerably higher than the level of the amputation have also been recorded. The reports of several cases in which the growth recurred follow:

CASE 4.—A girl aged 17 years had had symptoms for six months, on the basis of which a diagnosis of an osteogenic ossifying sarcoma was made. In the history it is stated that a resection of the femur could have been performed but that the functional result would not have been as good as that after amputation. A high amputation was therefore performed. Tissue removed at the level of amputation revealed no evidence of tumor. According to the pathologic notes, the main mass of the tumor was outside the periosteum. At the level of the adductor tubercle



Fig 7 (case 4).—Roentgenogram showing a dense shadow in the right side of the pelvis, the site of a huge recurrent tumor, in a patient who had a sclerosing sarcoma of the lower end of the femur.

above the medial condyle of the femur the marrow cavity was occluded. The periosteum at this level was roughened but not definitely lipped or raised. Ossification of the tumor, the age of the patient, the short duration of symptoms and the occlusion of the marrow cavity with sclerosis favored the diagnosis of osteogenic tumor of the sclerosing type. Occasionally a chondromyxoma at this site might show considerable ossification, but one would not expect so much sclerosis with involvement of the marrow cavity. The patient was operated on on Nov. 2, 1929. Roentgenograms made on May 31, 1930 (fig. 7), showed distinct evidences of recurrence, and the following note appears in the history: "This is the first time that recurrence has occurred in the stump when the resection was done through the middle of the femur." Sections of the marrow cavity were made at the time

of the amputation, and no tumor tissue was found. Within seven months the same type of tumor had recurred in the part of the shaft of the femur which was not removed. Roentgenograms of the chest were normal, but a definite ossifying mass could be demonstrated in the pelvis on the same side. We have seen masses in the groin and neck, but never a recurrence in the stump. This sarcoma ran a rapid course, terminating fatally five months after the time pain was first noted in the lower end of the right femur. A swelling could be palpated shortly after the pain appeared.

Although such a recurrence in the stump of the femur is rare after an amputation done through the middle third of the thigh for sclerosing sarcoma in the lower end of the femur and of the bones below the knee joint, local recurrence or extension in the region of the pelvis is more common in cases in which the tumor involves the upper end of the femur. In such cases amputation or disarticulation at the hip joint was formerly attempted, but without success. In the past decade no attempt at radical surgical intervention has been made in cases of sarcoma of bone in the upper third of the femur, since in the cases recorded in this laboratory for over forty years such attempts have been uniformly unsuccessful. The following history records such an unsuccessful attempt in the case of a sclerosing sarcoma in the upper third of the femur.

CASE 5.—A white youth aged 18 bruised his hip in a fall in December 1919, three months before he consulted a physician. Gradually the pain and stiffness about the hip increased. Swelling was noted, and constant pain and tenderness were experienced for three weeks. A roentgenogram revealed a density of the neck and head of the femur, with a slight periosteal reaction. On March 9, 1920, disarticulation of the hip joint was performed. When the gross specimen was examined a soft mass surrounded the neck and trochanter of the femur, which was collar shaped and covered with muscle. A cross-section of the portion of the femur involved revealed small areas of erosion in the cortical bone, and this erosion extended in places to the cartilage of the head of the bone. Areas of sclerosis were distributed among the grayish white areas of solid tumor tissue. The less dense portions were continuous with masses of tumor tissue which extended beneath the periosteum. The microscopic diagnosis was sclerosing osteogenic sarcoma of the upper end of the femur. Irregular spicules of osteoid material were distributed among solid sheets of proliferating osteoblasts. A recurrence was noted in the pelvis three months later. The patient died in July 1920, four months after the disarticulation.

INVOLVEMENT OF OTHER BONES

In some cases the question arises as to whether a second tumor is an independent growth or a metastatic one. Secondary deposits in other portions of the skeleton have been described repeatedly in cases of Ewing's tumor. In the various types of osteogenic sarcoma, however, metastasis of the tumor to other bones is extremely rare. In the

following three cases involvement of other bones in the skeleton occurred with sclerosing sarcoma primary in the lower end of the femur, the upper end of the tibia and the ilium, respectively.

CASE 6.—A white girl aged 18 injured her right leg ten months before admission to the hospital. Four months before pain and swelling appeared in the region above the knee. She continued to use the leg actively until two months before admission, when she was put on crutches to keep the leg at rest. The first roentgenograms were made after the appearance of the swelling (fig. 9). These showed a dense cloudiness in the marrow cavity of the femur extending 4 cm. above the condyle. There was an irregular periosteal reaction extending upward to about the junction of the middle third of the femur. These films were made in August 1925, and in October 1925 the sclerosis had extended up the marrow cavity of the

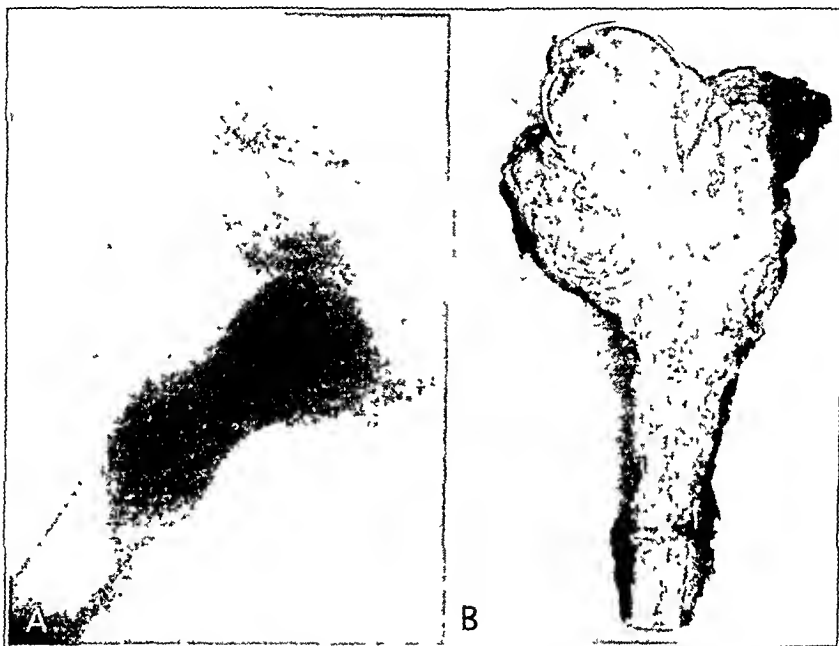


Fig. 8 (case 5)—*A*, roentgenogram, taken after symptoms of four months' duration, showing sclerosis of the marrow cavity in the neck and head of the right femur. There is a slight periosteal reaction about the neck of the femur. A disarticulation at the hip joint was performed. *B*, the gross specimen showing the extent of involvement of the upper end of the femur and the characteristic sclerosis of the marrow cavity.

femur with a large amount of new bone formation radiating at a right angle from the periosteal margin on the lateral side. The diagnosis on the basis of the roentgenographic picture was sclerosing osteogenic sarcoma. On October 28 Dr. Bloodgood performed an amputation through the middle of the right thigh. The lesion was explored before amputation, and frozen section confirmed the diagnosis of sarcoma. In January 1926 a bony swelling appeared in the region of the hyoid bone in the neck, which was attached to the hyoid bone and seemed fixed to the larynx. In April 1926 fluid was found in the pleural cavities. The patient died of pulmonary metastases on May 29.

CASE 7.—A white boy aged 11 years fell and injured his right knee in September 1933. A large black and blue area developed on the inner surface of the knee. Cold applications were applied, but the bluish discoloration did not disappear. There was no pain or swelling. The discoloration persisted for about one month and then cleared. During this time there was no loss of function of the right leg. About nine weeks before the present examination the patient commenced to limp. There was no swelling or pain in the leg. However, the patient complained of fatigue in each leg. One week later a swelling was noticed which was not discolored nor tender and seemed to have normal resistance. The limping continued, and the patient then noticed pain in the right leg on arising, which would disappear during the day. The swelling increased slightly. The patient was seen by a physician, who referred him to the hospital for application of a cast. This was done five weeks before our examination. At that time a diagnosis of subacute



Fig. 9 (case 6).—Roentgenograms showing sclerosis of the marrow cavity in the lateral view and periosteal extension of the tumor along the lateral margin of the lower end of the femur in the anteroposterior view.

osteomyelitis was made. The lesion was explored and curetted in June 1934. After the exploration the tumor grew rapidly, and the newly formed bone grew through the periosteum and extended into the soft parts (fig. 10). A diagnosis of osteogenic sarcoma was made, and an amputation was done in July 1934 through the thigh. After amputation the patient complained of severe pain and stiffness in the right arm. For a while no attention was paid to these symptoms, but in 1935 a roentgenogram disclosed a dense shadow in the right humerus in the same position as in the tibia at the diaphysial end of the bone, and in February 1936 the typical picture of a sclerosing sarcoma was found. In April 1937 the lesion in the shoulder is much larger, and the boy is rapidly losing ground (fig. 11).

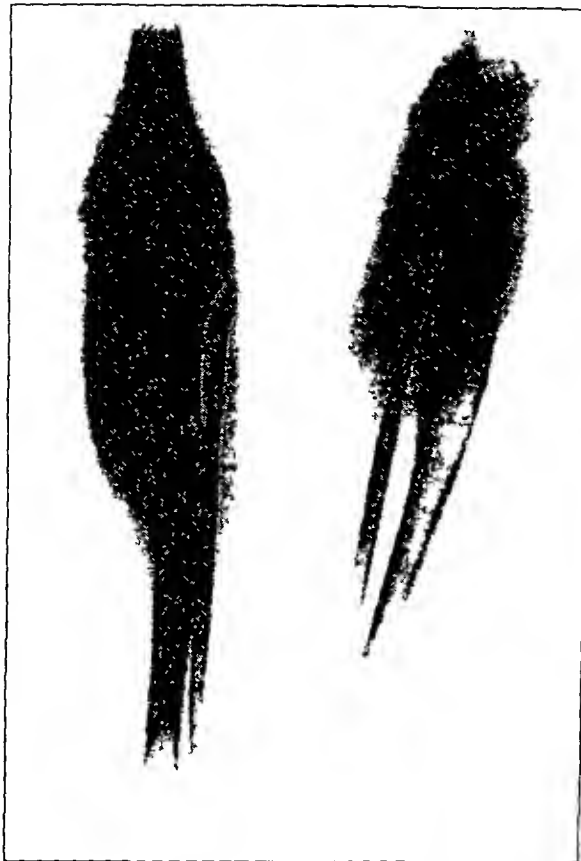


Fig 10 (case 7) —Roentgenograms showing a sclerosing sarcoma of the upper end of the tibia.

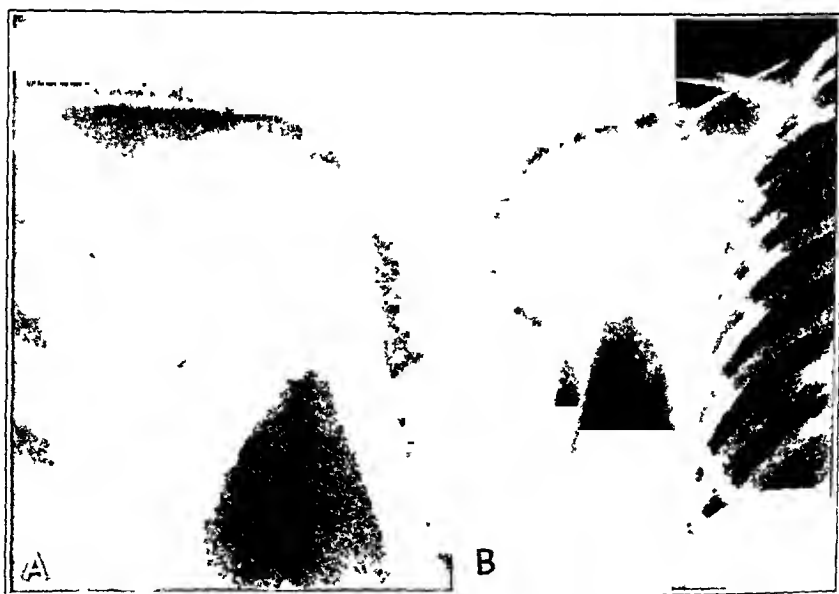


Fig. 11 (case 7) —*A*, a roentgenogram, taken in 1935, showing sclerosis of the marrow cavity in the neck of the humerus. *B*, a roentgenogram, taken in April 1937, showing extensive periosteal reaction and invasion of the soft parts. The patient was referred by Dr T P Loughery, of Germantown, Pa

CASE 8.—A white man aged 61 had no complaints except that of pain in his hip. On examination large palpable bony tumor masses were found in the region of the ilium over the sternum and ribs, and several nodular masses were felt protruding in the region of the calvarium (fig. 12). A specimen for biopsy was taken from the tumor in the sternum. The histologic structure was that of a typical sclerosing sarcoma. The tumor in the pelvis grew rapidly, and the patient died six months after the biopsy was done.

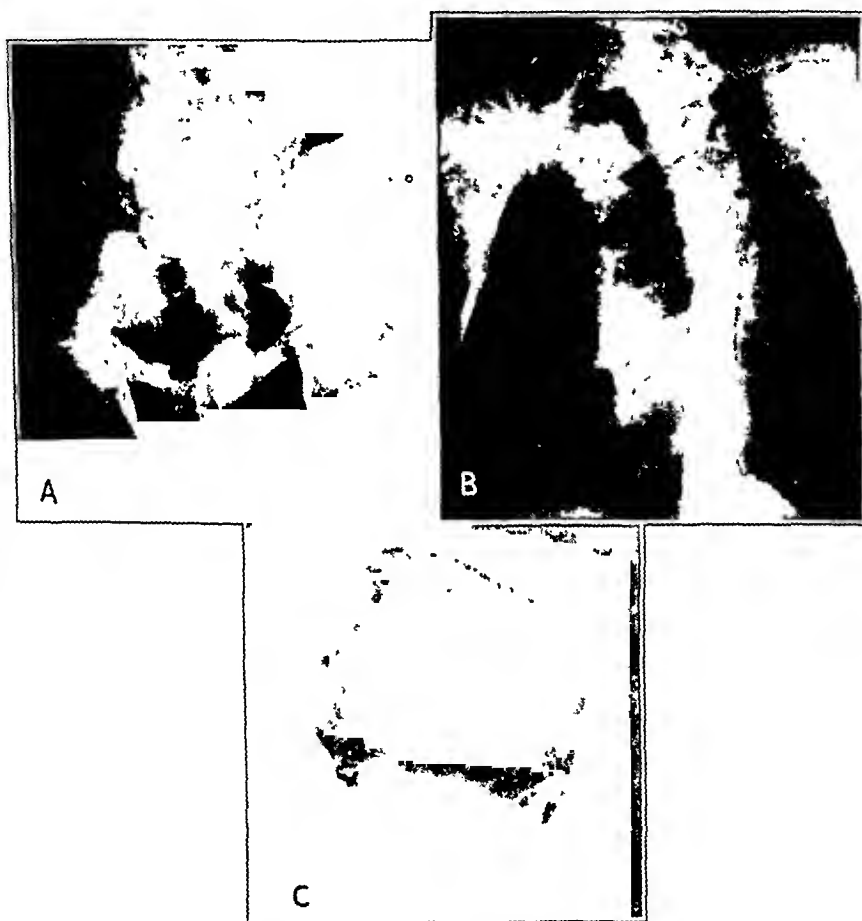


Fig. 12 (case 8).—Roentgenograms showing tumor masses in the right side of the ilium (*A*), the third and fourth ribs (*B*) and in the calvarium (*C*). The patient was referred by Dr. J. Atlee, Lancaster, Pa

IRRADIATION

Sclerosing osteogenic sarcoma is not a radiosensitive tumor. However, in cases of inoperable tumor in which pulmonary metastases have already occurred, when the tumor is situated in the bones of the pelvis or in the upper end of the femur, high voltage roentgen therapy may lessen the swelling and decrease the pain for several months. We have

no proof to date that irradiation will prolong life or cure the disease, and our evidence is not in favor of preoperative irradiation. Sometimes irradiation must be resorted to when consent for radical surgical intervention cannot be obtained.

CASE 9.—A white woman aged 23 was perfectly well until July 1931, when she began having what seemed to be sciatic rheumatism on the left side. She was treated for neuritis and arthritis until three weeks before the present examination. There were localized tenderness and pain over the left sacro-iliac joint, tenderness along the sciatic nerve and secondary scoliosis with convexity of the curve away from the side of the lesion. A tumor occupied a large part of the left lower quadrant, extending up to a point midway between the ilium and the umbilicus. The mass was found to be tender to pressure, and the pain was localized in the sacro-iliac area, traveling down the sciatic nerve. The roentgenogram showed a



Fig. 13 (case 9).—Roentgenogram showing an ossifying tumor in the right side of the pelvis in the region of the sacro-iliac joint.

sclerosing tumor occupying the left side of the ilium and the sacro-iliac region (fig. 13). There was much new bone formation with some radiating spicules. The patient was treated with high voltage roentgen radiation in 1933 and 1934. The pain was somewhat relieved for a period of three months, but the growth of the tumor continued. The patient died of metastasis to the lungs early in 1935.

CASE 10.—A white man 23 years of age injured the lower part of the femur on the inner aspect four months before examination. The diagnosis of a strained ligament was made by the family physician. One month before examination considerable pain was experienced, with some limitation of motion. At the time of examination considerable enlargement of the right knee was noted, the circumference measuring 45 cm. The skin over the swelling was tense and red; the swelling was tender. On roentgen examination a dense shadow was found in the marrow cavity, which extended throughout the lower third of the femur to the articular

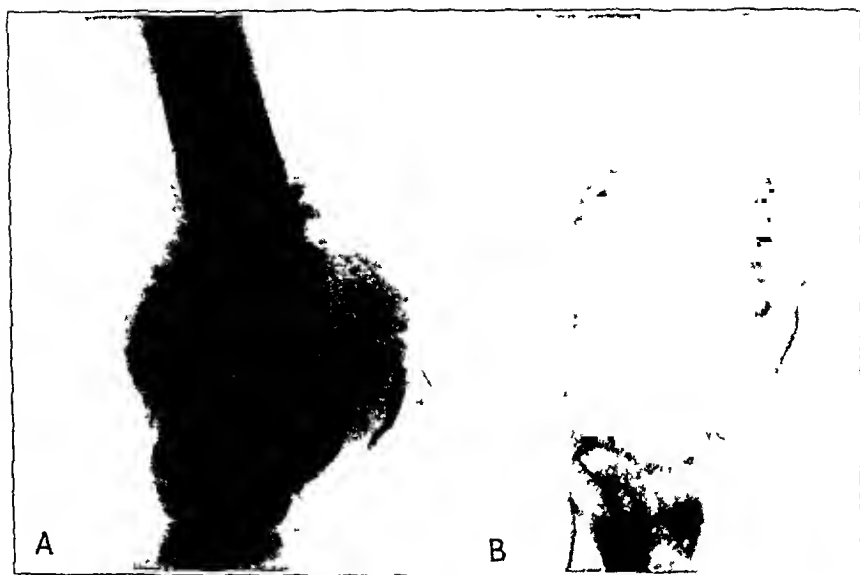


Fig. 14 (case 10).—*A*, a roentgenogram taken in October 1934, which formed the basis for a diagnosis of osteogenic sarcoma. The tumor filled the marrow spaces at the lower end of the femur and extended beneath the periosteum. There was a large soft part shadow above the patella. Between October 1934 and February 1935 the patient received high voltage roentgen therapy—a total dose of 3,840 roentgens. The swelling receded, and the pain was relieved. The ossifying mass, however, was not decreased in size, as shown in *B*.



Fig. 15.—Roentgenogram showing characteristic sclerosis in the lower end of the radius, produced by a sarcoma. The swelling was of only seven weeks' duration at the time this film was taken. There was little periosteal tumor reaction. Compare with figure 16.



Fig. 16.—Roentgenogram of a sarcoma of the lower end of the radius of the patient shown in figure 15. This film was made one month after figure 15 and only eleven weeks after the onset of symptoms. There was a pronounced periosteal reaction, and the bulk of the tumor was outside the bone. The characteristic sunburst appearance was present.



Fig. 17.—Roentgenograms of a sclerosing sarcoma three months after the onset of symptoms. The tumor invaded the cortical substance and cancellous bone throughout the upper end of the tibia extending to the joint surface. In spite of the extensive involvement of bone, there were relatively little periosteal reaction and practically no invasion of the structures surrounding bone.

cartilage (fig. 14). No periosteal lipping was noted. Just above the internal condyle the cortical bone was eroded. Shadows of masses, apparently dense, were visible in the soft parts along the sides of the femur. Since the patient's family would not consent to amputation, high voltage roentgen therapy was employed. Between October 1934 and February 1935 a total dose of 3,840 roentgens in divided doses over three fields was given. The pain was relieved, and the swelling about the knee was reduced. Despite these indications of improvement, the shadows increased decidedly. The patient died about six months after treatment was begun



Fig. 18—Roentgenogram of the knee joint of a white youth aged 20, who during May 1936 felt some pain in the right tibia just below the knee. The pain seemed worse at night. In December 1936 he visited a physician, and a diagnosis of tumor of the bone was made. Roentgen treatments were then started, the skin later becoming red and discolored. After the treatments the swelling had decreased somewhat. The patient lost 30 pounds (13.6 Kg.) during a short time. No metastases to the lungs were found. In the roentgenograms the lateral portion of the head of the tibia is sclerosed. The tumor has not invaded the soft parts, and there is no periosteal "sunburst." An amputation was performed through the middle of the thigh. Microscopically, variations and pleomorphism were noted in the cell structure, as well as the presence of large amounts of osteoid tissue. The tumor, however, on the whole was not very cellular, and new bone formation predominated.

COMMENT

A careful study of sclerosing osteogenic sarcoma in its earliest phases indicates that the most characteristic location of the tumor is neither in the periosteum nor in the subperiosteal regions but in the bone itself in its cancellous or cortical portions. The characteristic sunburst and periosteal manifestations so often stressed as diagnostically significant in the roentgenogram are late manifestations. Because of the rapid growth of the tumor, this mode of onset is often obscured.



Fig. 19.—Roentgenogram of a typical sclerosing sarcoma in the lower end of the femur in a boy aged 10. The dense triangle of new bone has the characteristic location of the shaft side of the epiphyseal line. There is a beginning periosteal reaction.

The tumor shown in figures 15 and 16 illustrates this point. In this case the tumor arose in the lower end of the left radius in a child of 7. The swelling was only of seven weeks' duration when the first roentgenogram was made on April 26, 1926 (fig. 15). In this film the metaphysis of the lower end of the radius is sclerosed, and there is little periosteal new bone. In the film made one month later, May

28, 1926, the characteristic sunburst of periosteal new bone is seen (fig. 16). In this case had the roentgen examination been postponed for a matter of a few weeks only, the origin of the tumor in the substance of the bone proper would not have been suspected.

From the standpoint of the histogenesis of the tumor it is not easy to decide whether this early manifestation within the bone, as seen in the roentgenogram, is due to the origin of the tumor in this region or to the fact that the tumor tissue invading bone tends to ossify earlier when there is an abundant supply of mineral salts furnished by normal bone. That the tumor may begin in bone is indicated by cases in which the bulk of the tumor is confined to bone in the relatively advanced stages. Such a case is illustrated in figure 17, which shows fairly extensive involvement of the head of the tibia with relatively little periosteal reaction. Similar cases are illustrated in figures 18 and 19. The histologic structure of the tumor also suggests such an origin. In young persons ossifying sarcoma begins beneath the periosteum, and cartilage arising from remnants of the primitive perichondrium is often found in the tumor. In adults ossifying sarcoma may develop from the region of the periosteum, and when this occurs the bulk of the tumor is usually found outside the bone. The histologic structure of these periosteal tumors in adults differs from that of typical sclerosing sarcoma in containing large amounts of fibrous tissue. In contrast to this, malignant osteoblasts and osteoid spicules usually predominate in the section from a typical sclerosing sarcoma.

TORSION OF THE FALLOPIAN TUBE IN THE VIRGIN

REPORT OF A CASE AND REVIEW OF THE LITERATURE

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Torsion of the fallopian tube is not an exceedingly rare condition. Since the first report of a case by Bland-Sutton¹ in 1890, followed by one by Delbet² in 1892, there have appeared reports of many cases in which the torsion was due to various pathologic conditions of the adnexa (pyosalpinx, hydrosalpinx, hematosalpinx and tumor). In many cases torsion of the tube was associated with torsion of the corresponding ovary. Anspach,³ who reviewed the literature in 1912, collected reports of eighty-five cases of torsion of the diseased tube. In most cases the tube was transformed into a cystic tumor, thus creating conditions that favor its twisting around the pedicle. Eastman⁴ in 1927 reviewed the literature on torsion of hydrosalpinx. This kind of torsion of the pathologic tube is referred to in the German literature as *Tubentstieldrehung* in contrast to *Tubentorsion*, which means torsion of the previously normal tube. These terms may be translated into English as "torsion of the tubal pedicle" and "torsion of the tube." This distinction, which appears to us essential, is based on the fact that the normal fallopian tube does not possess a proper pedicle, and the existence of a pedicle is identical with the cystic transformation of the tube (hydrosalpinx and pyosalpinx).

Torsion of the undiseased fallopian tube is of much rarer occurrence. The first observations of torsion of normal adnexa in a virginal genital

From the Departments of Surgery and Pathology of Mount Sinai Hospital.

1. Bland-Sutton, T.: Salpingitis and Some of Its Effects, *Lancet* 2:1146-1148 and 1206-1209, 1890.

2. Delbet, P.: Torsion du pédicule dans un cas de salpingite, *Bull. Soc. anat. de Paris* 67:300-302, 1892.

3. Anspach, B. M.: The Torsion of Tubal Enlargements with Especial Reference to Pyosalpinx, *Am. J. Obst.* 66:553-595, 1912.

4. Eastman, N. J.: Torsion of Hydrosalpinx, *Surg., Gynec. & Obst.* 45:143-147, 1927.

tract were reported by Stark⁵ in 1911, Norris⁶ in 1911, Cassidy and Norbury⁷ in 1911, Auvray⁸ in 1912 and 1913 and Schweitzer⁹ in 1918.

Stark observed torsion of the left tube in a 46 year old virgin. Her past history was essentially irrelevant. She was suddenly taken ill with a severe attack of abdominal pain localized in the left iliac region. When the abdomen was opened a few blood clots were found lying loosely in the pelvis. The left tube was twisted into three complete turns from right to left. On the right side a dermoid cyst with sebaceous material and hairs was found. Microscopic examination did not reveal any signs of pregnancy. The case of Norris was that of a 19 year old virgin. There was complete torsion of the right ovary with secondary involvement of the tube. Cassidy and Norbury reported a case of torsion of the entire left adnexa in a girl 11 years old. In 1912 Auvray wrote a monograph on torsion of the normal adnexa and reported a case of torsion of the right normal tube and ovary in a girl 14½ years old. In 1913 he published the report of a case of isolated torsion of the right tube in a virgin 28 years old. For two years at intervals she complained of cramplike pains in the right lower abdominal quadrant. At operation a mass the size of a tangerine was found in the pelvis. The tip of the appendix was attached to the mass, which consisted of the right tube twisted twice and distended with bloody fluid. The ovary and the opposite adnexa were normal. Pathologic examination revealed mainly extensive necrosis and hemorrhage. In the less affected areas there were some inflammatory changes consisting mainly of accumulations of round cells and occasional giant cells. These changes were considered secondary. The appendix was undiseased. In 1918 Schweitzer called the attention of the German medical profession for the first time to torsion of a normal tube. His case was that of a single girl 21 years old. (For details, see case 2 in the table.) In the ten years from 1908 to 1918 Schweitzer could not find a similar case in the large material of the University Clinic of Leipzig. We found only occasional similar reports in the following years up to about ten years ago. Since this time the medical literature shows an increasing number of reports dealing

5. Stark, J.: Acute Torsion of Normal Appendages with Hematosalpinx, *J. Obst. & Gynec. Brit. Emp.* **19**:258-260, 1911.

6. Norris, C. C.: Torsion of the Normal Uterine Appendages: Report of a Case, *Am. J. Obst.* **63**:850-854, 1911.

7. Cassidy, M. A., and Norbury, L. E. C.: Torsion of the Left Broad Ligament and Fallopian Tube in a Child, *Lancet* **1**:98-99, 1911.

8. Auvray, M.: (a) De la torsion spontanée de la trompe et de l'ovaire normaux, *Bull. Soc. d'obst. et de gynéc. de Paris* **1**:727-731, 1912; (b) Nouveau cas de torsion spontanée de la trompe saine, *Arch. méns. d'obst. et de gynéc.* **2**:97-104, 1913.

9. Schweitzer, B.: Isolierte Torsion der normalen Tube, *Zentralbl. f. Gynäk.* **42**:25-33, 1918.

Cases of Torsion of the Undiseased Fallopian Tube in Virgins

Year	Author	Age of Patient	Clinical History	Preoperative Diagnosis	Operative Findings	Pathologic Examination
1913	Auvray ¹⁰	23	Cramplike pains in right lower abdominal quadrant at intervals for 2 yr.; last attack more severe; temp. 39° C. (102.3° F.); menses since 14 yr.; fairly regular; dysmenorrhea for past 6 mo.; past history irrelevant	Appendicitis	Mass about the size of a tangerine in pelvis; right tube twisted twice and distended with bloody fluid; tip of appendix attached to mass; ovary and opposite adnexa normal	Marked necrosis and extensive hemorrhages; some inflammatory changes in less destroyed areas; many round cells and occasional giant cells; no polymorphonuclears; inflammatory changes considered secondary; ovary and appendix normal
1918	Schweltzer ⁹	21	Sudden onset of severe pain in lower part of abdomen; painful micturition; 5 wks. later similar attack at menstruation	Twisted ovarian cyst	Left adnexa: cystic tumor, size of an apple, bluish red, in adhesions with omentum and lateral abdominal wall; left tube twisted twice in middle portion; ovary normal; right adnexa: tube about twice normal length; otherwise normal	Severe circulatory disturbances; diffuse hemorrhagic infarction of wall of tube; venous circulation particularly affected; veins and capillaries maximally distended and partly ruptured; sacrosalpinx haemorrhagic Cause: torsion of tube Not reported
1922	Hansen ²⁰	14	Sudden onset of severe pain in right lower abdominal quadrant; first attack after exercise; vomiting; tenderness and rigidity; W.B.C. 30,000; temp. 37.8° C. (100° F.); past history irrelevant	Appendicitis with abscess formation	Torsion of right tube in its isthmie portion (360 degrees); tube tense, the size of a hen's egg and bluish black; fibrilated end closed; small follicular cyst on ovary; opposite adnexa normal; appendix long and thickened in distal position	No histologic report; blood clot in lumen of tube; wall congested and thickened; hemorrhages into wall; no evidence of inflammation
1925	Davies ¹⁸	19	Acute pain in right iliac fossa; continuous vomiting; patient menstruating the day of incident	Appendix slightly congested; right tube black and swollen to size of small vistoria plum; twisted clockwise; mesosalpinx abnormally long; both ovaries normal	Dense hemorrhage in which remains of wall of tube could be seen
1925	Rogers ¹⁹	16	Acute pain in lower part of abdomen of 1 days' duration; vomiting	Ampullary portion of right tube black, swollen and twisted on its mesosalpinx; left tube also underwent torsion but to a less extent	Serosa completely disappeared; muscularis infiltrated with fresh and old hemorrhages; veins markedly dilated; marked edema; degeneration of epithelium; tubal lumen extremely dilated and filled with blood clots; no evidence of fresh or old inflammatory lesion; appendix normal
1926	Darner ¹⁶	13	Sudden onset of colicky pain in right iliac fossa; nausea; no vomiting; rigidity and tenderness in entire right lower quadrant; W.B.C. 14,800; menstruation began 2 mo. before hospitalization; since then amenorrhea	Acute appendicitis with abscess	300 cc. of a blood-tinged fluid in peritoneal cavity; appendix normal; distal third of right tube greatly distended and bluish black; fibrine markedly swollen; small hydatid cyst attached to mass; mesodial and proximal third of tube twisted clockwise 3½ times; ovary and opposite adnexa normal	No report
1926	Gillies ²²	23	Acute pain in left iliac fossa; vomiting; pain on micturition for 3 days	Appendicitis (most probable)	Abundant free fluid in pelvis; left tube swollen, nearly black and twisted twice around its long axis; ovary and right adnexa normal	Grossly, no morphologic details recognizable (blood clots); microscopically, mostly necrotic tissue; abundant leukocytic infiltration; in less destroyed places, epithelium resembled that of the tube
1927	Ffolie ¹²	10	Sudden onset of severe pain in lower part of abdomen; vomiting; tenderness throughout abdomen; most marked in right iliac fossa; temp. 37.1° C. (98.8° F.)	Appendicitis with perforation (?)	Abundant free blood in peritoneal cavity; appendix long and slightly injected; at right of uterus a black mass the size of a tangerine attached to a pedicle, distinctly twisted twice clockwise	Grossly, tube not recognizable; tissue soaked with blood; blood vessels distended; some small groups of lymphocytes; peritoneal endothelium well preserved; mucosa not recognizable; diagnosis: stasis per magna tubae cum haemorrhagia
1928	Vigghold: Acta obst. et gynec. Scandinav. ⁷ 327, 1928.	17	Sudden onset of abdominal pains in right iliac fossa; no nausea or vomiting; tenderness over McBurney's point; temp. 38.2° C. (100.7° F.); menses since 16 yr.	Acute appendicitis	Appendix normal; orange-sized tumor of tube twisted 3 times clockwise around its pedicle; no adhesions; ovary and left adnexa normal	

Year	Author	Case	Notes	Diagnosis	Remarks
1920	Koster 17	10	Sudden sharp pain in lower part of abdomen; frequent micturition; no nausea or vomiting; menses since 14 yr.; dysmenorrhea; menstruation at time of torsion	Ovarian cyst with twisted pedicle	Serosanguineous fluid in peritoneal cavity; right tube twisted 1 1/2 turns on the inner 3d; distal to black and tense; bluish free; left adnexa and appendix normal
1922	Gabe 13	13	Dull pain across lower part of abdomen; nausea and vomiting; W.B.C. 18,000; temp. 100 F.; marked tenderness over McBurney's point; menses since 11 yr.; fairly regular	Acute appendicitis	Free blood-tinged fluid; appendix: tube size of an orange; twisted 2 1/2 turns (4 cm. from uterus); ovary and left adnexa normal
1920	Debray: Ann. d'anat. path. 6: 125-126, 1920	15 1/2	Attack of severe abdominal pains in right iliac fossa at end of regular menstrual period; past history unimportant	Acute appendicitis	Some serosanguineous fluid in the cavity; right tube twisted 3 times clockwise; appendix slightly injected; ovary and left adnexa normal
1930	Walawelski: Zentralbl. f. Gynäk. 54: 861-867, 1930	21	Since childhood occasional pains in lower part of abdomen; severe attacks independent of menstruation of 1 year's duration; menses since 17 yr.	Appendicitis	Apple-sized bluish tumor, cystically distended; right tube twisted clockwise 360 degrees
1932	Sorrel, Obehtur and Loutsch: Bull. et mem. Soc. nat. de chir. 35: 909-913, 1932	13	Several attacks of abdominal pains and vomiting; first attack at onset of menstruation 3 mo. previously; past history, appendicitis with abscess and spontaneous resorption when 9 yr. old	Appendicitis; torsion of adnexa (?)	Serosanguineous fluid in peritoneal cavity; appendix normal; black tendent and contralaterally twisted right tube; ovary and left adnexa normal
1932	Rieard 23	14	Severe attack of pain in right lower quadrant repeated the following day with vomiting; temp. 38.2 C.; menses regularly since 5 months before present illness	Acute appendicitis	Abundant serous, slightly bloody fluid in peritoneal cavity; appendix swollen, injected and definitely distended 4 times in its ampullar portion, forming a black mass; ovary and left adnexa normal
1932	Cutcel 31	19	Sudden onset of pain in left lower quadrant; vomiting; temp. 38 C. (100.4 F.)	Torsion of left ovarian cyst	Distended infarcted left tube twice contralaterally; appendix injected; ovary and right adnexa normal
1933	Block and Michael 30	13	Awakened from sleep by sharp pain in left lower quadrant; nausea; 15,000; 82% polymorphonuclears; no fever; past history unimportant	Acute appendicitis	Small amount of free blood in peritoneal cavity; appendix fairly normal; right tube dark red, gangrenous and size of a hen's egg; twisted 2 1/2 turns contralaterally; left adnexa normal
1931	McEalern: Brit. M. J. 1: 190-192, 1931	14	Pains in right lower quadrant of 4 days' duration; vomiting; temp. 98.8 F.; attacks of pain in right iliac fossa since age of 2; menstruated 3 times; fourth menses appeared 24 hr. after operation	Acute appendicitis	Right tube much enlarged; twisted 2 complete turns in antileokwisc direction; hemorrhagic effusion into wall and lumen; ovary not involved; appendix mildly inflamed
1935	Lepoutre: Bull. Soc. Obst et de Gynec. 24: 388-389, 1935	15	Sudden onset of severe abdominal pain in lower left quadrant; nausea; bile vomiting; abdomen slightly rigid; tender throughout; menses appeared shortly after operation	Torsion of left ovarian cyst	Left tube black and twisted 2 complete turns; ovary not involved in torsion; contains small cysts; right adnexa normal

Fibrous tissue and muscle bundles separated by multiple hemorrhages; veins distended; mucosa unresorbable; diagnosis: hemorrhagic infarction

Extravasation of blood into the tissues due to mechanical strangulation; no evidence of organic disease (3 photomicrographs)

Normal portion of the tube near uterus; zone of torsion; external portion consisting of black, markedly swollen tubal mass; fibrillated but recognizable; contain a small hemorrhagic cyst; ostium patent; blood clots; no evidence of old or recent inflammatory lesions

Tissue of the tube histologically normal in places; in other places, complete hemorrhagic infarction

Histologic picture confirmed gross findings that tube was not diseased

Layers of the wall dissociated by a recent hemorrhage; on the surface blood cells; no evidence of old or recent inflammatory process

Lesions of a hemorrhagic infarction; no evidence of previously existing pathologic process

Almost total destruction of mucosa of tube; edema and hemorrhages of the wall; blood vessels engorged; large area of blood clots; picture that of cellular destruction due to strangulation rather than inflammatory process

Hemorrhagic effusion as the result of torsion; no evidence of pregnancy

Abdominal ostium of the tube patent; histologic examination not reported

with torsion of the undiseased adnexa. Especially numerous are the reports of French authors, who consider torsion of normal tubes a definitely established clinical and pathologic entity of more frequent occurrence than is usually thought of (Auvray,⁸ Michon,¹⁰ Caraven,¹¹ Fiolle¹² and others). Most of these cases occurred in virgins. Together with Gabe,¹³ we wish to make a sharp distinction between the tube of a virgin and that of the married woman. Beyond the state of virginity and after abortion, pregnancy or the puerperium there are too many possibilities of infection (specific and nonspecific) and mechanical derangements which may have an effect on the structure and the function of the tube. They render the exact determination of the "normality" of the twisted tube impossible. On the other hand, the mere fact of virginity is not sufficient evidence that the tube was undiseased before torsion. In fact, Anspach collected reports of thirteen cases of torsion in nonmarried women ranging in age from 18 to 49. On operative inspection or histologic examination, all the tubes showed marked pathologic changes other than those due to torsion. In the reports of four cases we found the remark "virgin"; in others, only "single" or "unmarried." Anspach expressed the belief that torsion of a normal tube is impossible and that in cases of torsion in which the tube appears to be normal the condition is the result of an unrecognized salpingitis and hydrosalpinx following an acute exanthema, vulvovaginitis or an attenuated tuberculosis in childhood. In recent time Thorek¹⁴ supported this view by presenting the report of a case of torsion of the right fallopian tube in a 14 year old girl who was a virgin. At operation the periappendical structures, the parovarium and the right tube were found to be inflamed. The left ovary was greatly enlarged and cystic. Sections from the tube showed chronic and subacute salpingitis. In reporting this case, Thorek stated that few such cases had been described in the literature. In fact, in most of the cases of twisted virginal tubes the existing pathologic process was considered merely the result of torsion and strangulation.

10. Michon, L.: Le volvulus des annexes saines (à propos de 5 cas personnels), *Gynéc. et obst.* **21**:103-119, 1930. Michon, L., and Trillat, P.: Volvulus d'une annexe saine. *Lyon chir.* **28**:648-651, 1931.

11. Caraven, J.: Torsion des annexes normales avec hématoécèle pelvienne, *Bull. et mém. Soc. nat. de chir.* **53**:550-558, 1927.

12. Fiolle, J.: Torsion annexielle avec inondation péritonéale hémorragique chez une enfant de dix ans. (A propos de la valeur diagnostique de la contracture abdominale), *Bull. et mém. Soc. nat. de chir.* **53**:1238-1241, 1927; Torsion des annexes saines, *ibid.* **55**:785-787, 1929.

13. Gabe, W. E.: Torsion of the Undiseased Fallopian Tube, *Arch. Surg.* **18**: 1304-1314 (April) 1929.

14. Thorek, M.: Torsion of Fallopian Tube in Virgin, *M. J. & Rec.* **125**:470-473, 1927.

Marked disagreement prevails among the authors as to the real frequency of torsion of an undiseased tube. In 1921 Smith and Butler¹⁵ were able to collect reports of only fourteen cases of torsion of normal adnexa in females at any age and only three cases of the isolated torsion of a normal tube in nulliparous women (Stark,⁵ Auvray,⁸ Schweitzer⁹). Darner¹⁶ in 1926 reported a case of torsion of a normal fallopian tube in a 13 year old girl. Reviewing the literature, he found reports of only twelve cases of torsion of a normal tube in females at any age. Only five of them occurred in women who had never been pregnant. Darner considered primary torsion of the normal tube an "exceedingly rare" condition. In 1929 Koster¹⁷ found reports of eleven authentic cases of primary torsion of supposedly normal tubes in nulliparous women (Davies,¹⁸ Auvray,⁸ Schweitzer,⁹ Rogers,¹⁹ Hansen,²⁰ Stark,⁵ Darner,¹⁶ Jefferson,²¹ Gillies,²² Gabe¹³ and Heil²³). Even a few of these cases appear to us questionable, and the case of Heil does not belong in this group. In Heil's case the ovary was involved in the torsion, and on the opposite side there was a dermoid cyst with beginning torsion of the pedicle.

Downer and Brines²⁴ were able to find in the literature in 1931 reports of only six cases of twisted, otherwise normal fallopian tubes (Schwartz,²⁵ Koster,¹⁷ Hansen,²⁰ Rogers,¹⁹ Darner¹⁶ and Gabe¹³). We would exclude from this list the case of Schwartz, since in his case (that of a girl 16 years old) the opposite left tube was not normal. Its distal end was cystically distended, so that a bilateral salpingectomy was required. Shute,²⁶ who in 1932 commented on cases of adnexal

15. Smith, R. R., and Butler, W. J. · Concerning Torsion of the Uterine Adnexa Occurring Before Puberty, *Am. J. Obst. & Gynec* **2**:507-521, 1921

16. Darner, H. L. · Torsion of the Normal Fallopian Tube, *Am. J. Obst. & Gynec.* **11**:368-377, 1926

17. Koster, H. · Torsion of Normal Fallopian Tube, *Am. J. Surg* **7**:67-74, 1929.

18. Davies, D. J. · Torsion of Fallopian Tube, *Brit. M. J.* **1**:657, 1925

19. Rogers, L. · Torsion of Fallopian Tube, *Brit. M. J.* **1**:778, 1925

20. Hansen, A. · Tubentorsion mit Haematombildung und ihre Aetiologie, *Zentralbl. f. Gynak.* **46**:707-708, 1922

21. Jefferson, J. C. · Torsion of Fallopian Tube, *Brit. M. J.* **1**:55, 1926.

22. Gillies, J. C. · Torsion of Fallopian Tube, *Brit. M. J.* **1**:187, 1926.

23. Heil, K. · Ein Fall von Stieldrehung der Tube bei virginellem Genitaltraktus, *Zentralbl. f. Gynak.* **45**:498-499, 1921.

24. Downer, F. G., and Brines, O. A. · Torsion of Undiseased Uterine Adnexa in Virgins, *Am. J. Obst. & Gynec* **21**:665-671, 1931.

25. Schwartz, J. · Beitrag zum Vorkommen der Eileiterdrehung, *Zentralbl. f. Gynäk.* **46**:1959-1961, 1922

26. Shute, E. · Comments on Torsion of Adnexa Report of Illustrative Cases, *Am. J. Surg* **16**:490-500, 1932

torsion under every condition, reported six cases of his own. He stated that in fifty-three reported cases fairly good evidence was found that the tube involved was normal.

Regad²⁷ published several instructive and complete expositions on this subject and in 1933 summarized his conclusions based on the two hundred and one cases reported up to date, as shown in the following tabulation:

Relative Frequency of Torsion of the Fallopian Tube

Torsion of undiseased tube.....	24 per cent
(Histologic examination in only 8 per cent)	
Torsion of the hydrosalpinx.....	18 per cent
Torsion in hernial sac.....	14 per cent
Torsion of salpingitis, tubal pregnancy or twisted tumor	13.5 per cent
Torsion in the course of pregnancy.....	12 per cent
Torsion associated with appendicitis, fibromas or cyst of the ovary.....	9.5 per cent
Torsion followed by spontaneous amputation.....	5 per cent
Torsion, bilateral (diseased and undiseased).....	4 per cent

Frequency According to the Genital Activity

Before puberty	20 per cent
During the genital activity of women.....	80 per cent
These 80 per cent are distributed as follows:	
Virgins	33 per cent
Nulliparous women	25 per cent
Pregnant women	24 per cent
Multiparous women	18 per cent

Frequency According to the Age

In babies and infants.....	5 per cent
Between 10-13 years.....	16 per cent
Between 13-22 years.....	44 per cent
Between 22-35 years.....	25 per cent
Between 35-49 years.....	10 per cent

Side Affected

Kind of Torsion

Right	68 per cent	Clockwise on the right side.....	62 per cent
Left	32 per cent	Anticlockwise on the left.....	38 per cent

Mosettig²⁸ reviewed the German literature in 1933 and traced fourteen cases of torsion of a supposedly normal tube. Of these, only the cases of Schweitzer,⁹ Hansen²⁰ and Rueder²⁹ occurred in a virginal genital tract.

27. Regad, J.: La torsion des trompes utérines, *Gaz. d. hôp.* **106**:557-562, 1933; *Etude anatomo-pathologique de la torsion des trompes utérines*, *Gynéc. et obst.* **27**:519-535, 1933.

28. Mosettig, E.: Zur Kasuistik isolierter Tubenstieldrehungen, *Arch. f. Gynäk.* **154**:421-431, 1933.

29. Rueder: Drei Fälle von Stieldrehung der Tube bei normalem virginellem Genitaltractus, *Zentralbl. f. Gynäk.* **45**:45, 1921.

In the same year (1933) Block and Michael³⁰ reported a case in a girl 13 years old, similar to the case we are reporting in this paper. In reviewing the literature they do not mention two cases reported by the Italian author Caucci³¹ in 1932. Caucci reported six of his own cases. Two of them were cases of isolated torsion of the tube in two virgins, both 19 years old.

In comparing all these reviews we notice considerable divergence in the statements concerning the occurrence of the reported condition. The terms used in describing isolated torsion of the vaginal or undiseased tube vary from "not infrequent" to "exceedingly rare." What are the reasons? This divergence may be partly due to an incomplete review of the literature. But it seems that the more important factor is the varying individual conception of the authors as to the "normality" of the twisted tube. If we were to analyze all reported cases with the necessary criticism, we should be forced to admit that a large number of reports lack the proof that the organ was undiseased before the torsion. In more than half of the reported cases a histologic examination is missing; many do not mention the condition of the ovary on the same side and of the adnexa on the opposite side; still others give an unsatisfactory past history from which a venereal infection cannot be excluded. In many cases it is difficult, even impossible, to decide whether or not the tube was normal before torsion. In the cases in which there is advanced necrosis of the wall even a most careful histologic examination may fail to detect mild inflammatory changes. The hemorrhagic infarction as the result of torsion and strangulation may hide to some degree the underlying pathologic process of the wall of the tube.

We recently had the opportunity to observe and study a case of isolated torsion of the fallopian tube in a girl 10½ years old. We report this case because of its rarity and in order to discuss the difficulties in deciding whether or not the organ was undiseased before torsion. And this even in a case where there is no doubt of existing virginity.

REPORT OF CASE

M. L., a white girl aged 10½ years, was referred to the Mount Sinai Hospital on Aug. 19, 1935, with a diagnosis of acute appendicitis. She gave a history of being seized with a severe pain in the right lower abdominal quadrant two days previous to hospitalization. It was the first time she had had such an attack. The pain was gradually subsiding. She was nauseated but did not vomit. Her previous history was irrelevant. She had had measles many years before the present illness and an attack of scarlet fever two months before. The scarlet fever

30. Block, F. B., and Michael, M. A.: *Torsion of Normal Fallopian Tube*, *Am. J. Obst. & Gynec.* **26**:268-270, 1933.

31. Caucci, A.: *La torsione degli annessi uterini normali (sei osservazioni personali)*, *Policlinico (sez. chir.)* **39**:213-228, 1932.

was mild, and the rash subsided in twenty-four hours. The child made an uneventful recovery without any complications. There was no history of genital trouble or vaginal discharge, and the menses had not yet begun.

Physical examination revealed a fairly well developed and well nourished white girl 10 years of age, who appeared acutely ill. Her face was flushed. The temperature was 101.6 F., the pulse rate 132 and the respiratory rate 24. The abdomen was not rigid but was very tender to pressure in the right lower quadrant. The head, neck and chest were normal. Vaginal smears were done as a routine and showed no evidence of gonococci. Smears and cultures of material from the

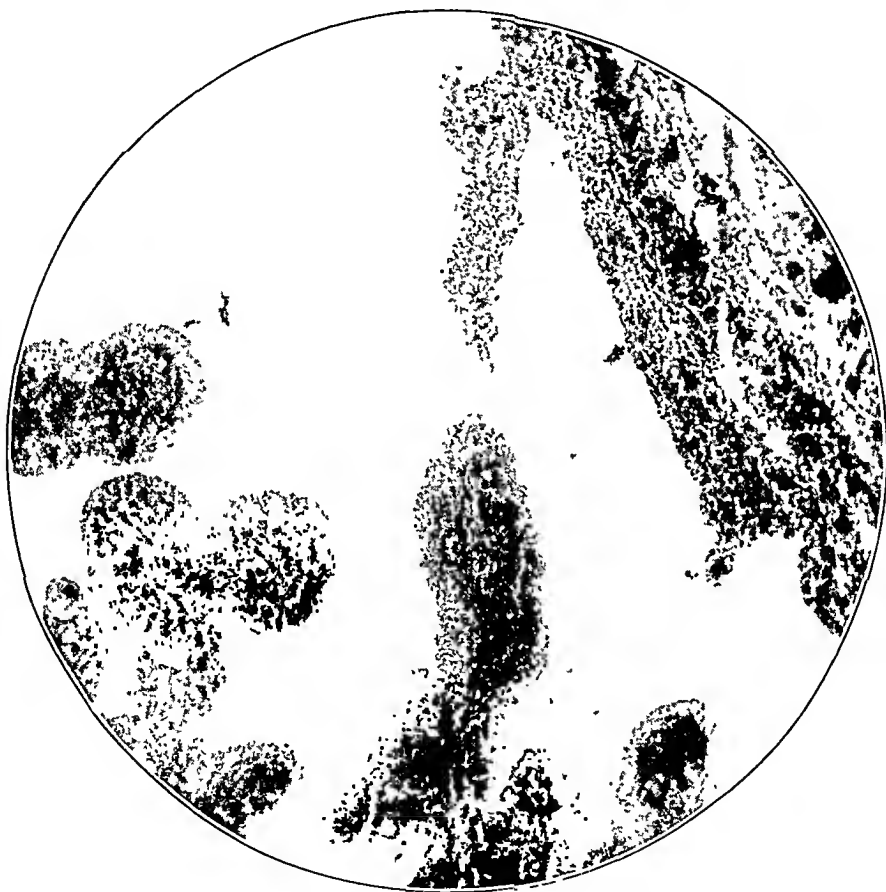


Fig. 1.—Low power photomicrograph showing hemorrhagic infarction of the tube. Note the diffuse hemorrhages extending into the folds. The epithelial lining is completely destroyed.

nose and throat were negative for *Bacillus diphtheriae* and hemolytic streptococci. The white cell count was 18,200, with 82 per cent polymorphonuclear leukocytes. The urine showed a faint trace of albumin. The diagnosis of acute appendicitis was confirmed, and the child was operated on immediately.

When the abdomen was opened through a muscle-splitting incision (Dr. B. Sayre), about 50 cc. of a blood-tinged fluid escaped. The appendix was injected and adherent to the omentum. Appendectomy was done, and the pelvis was

explored. In the hollow of the sacrum a large mass was palpable. This was finally brought up into the incision with some difficulty, and a black mass about the size of a large pear was revealed. The mass was followed down and found to be the right fallopian tube, which had twisted on itself in the clockwise direction with three complete turns. Its fimbriated end could not be demonstrated. The right ovary was in normal position and not involved in the torsion. It appeared slightly enlarged and had a few small cysts, which were punctured. The tube was untwisted and removed in the usual manner. Further exploration revealed an infantile uterus and a perfectly normal adnexa on the left side. The abdomen was closed without drainage, and the patient made an uneventful recovery, going home on the fifth postoperative day.

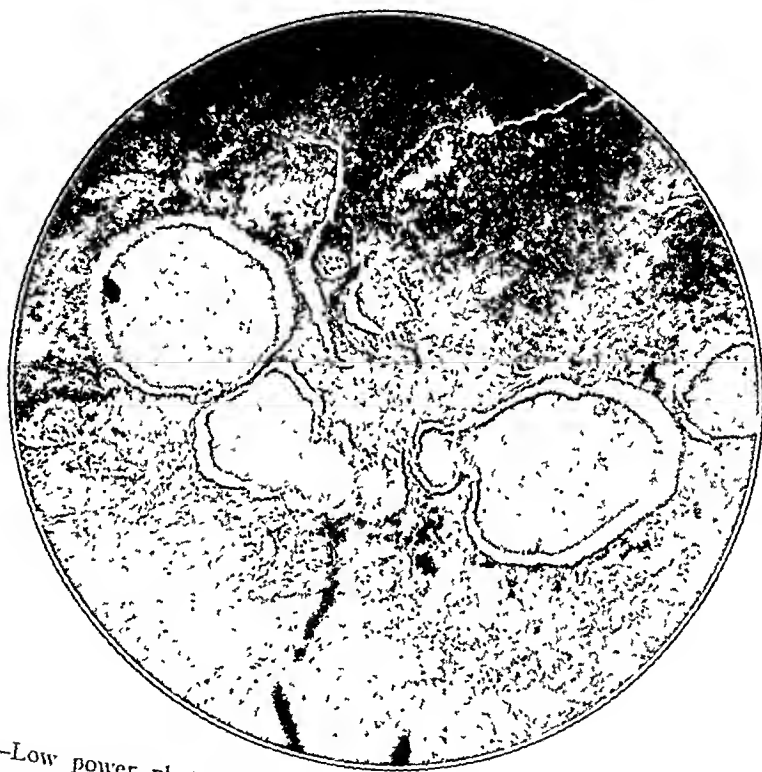


Fig. 2.—Low power photomicrograph showing hemorrhagic infarction of the tube. Part of the wall shows markedly distended capillaries and blood vessels with partly ruptured walls.

Pathologic Examination (Dr I Davidsohn and Dr. L. Blum).—Gross: The tube consisted of a cystic mass which measured about 85 by 42 by 13 mm. Its wall was a hemorrhagic membrane measuring from 1 to 2 mm. in thickness. The sectioned surface showed clotted blood, which was intimately connected with the wall and which could be separated from it only with considerable difficulty. No further morphologic details could be recognized grossly. The appendix measured 30 mm. in length and 17 mm. in the largest circumference. The serosa was markedly injected and showed evidences of adhesions. The lumen was patent and empty except for the tip, where it was occluded for a distance of 3 mm. The mucous membrane was somewhat edematous and showed occasional petechiae.

Was this case one of torsion of a normal fallopian tube in a virgin? The large balance of evidence favors the assumption of the integrity of the tube before torsion.

In favor of it are: (1) the age of the patient, (2) the occurrence before the onset of menstruation, (3) normal adnexa on the opposite side, (4) no history of vulvovaginitis in childhood and (5) mild acute exanthemas (measles and scarlet fever). Against it are: the findings of the closed fimbriated end and occasional accumulations of round cells on microscopic examination.

In the case reported we see how the overwhelming balance of evidence speaks for the integrity of the tube before torsion, and yet a definite determination is not possible, in spite of the careful histologic examination. We emphasize once again the importance as well as the difficulties of making the histologic examination. It is the most certain criterion for the integrity of the tube before torsion. Chastenet de Géry and Lacroix³⁴ reported a case of tubal torsion in a woman 29 years old. The tubes appeared perfectly normal on gross inspection, but only on microscopic examination were they found to be tuberculous.

In reviewing the literature we collected the reports of cases which appeared to us the most authentic ones of isolated torsion of the undiseased virginal tube and tabulated the data (see table). As to torsion of the doubtless pathologic virginal tubes, we refer to the cases collected by Anspach³ and the case reported by Thorek.¹⁴ Recently Askey³⁵ and Caucci³¹ reported cases of torsion of pathologic tubes in virgins. Since we considered only torsion of the virginal tube, numerous cases reported during pregnancy are not included.

We do not intend to add to the existing definition of the "normal" tube another one, but we wish to make a few suggestions as to the points to be considered in giving an authentic report and in discussing torsion of the normal tube. The following points seem to us important:

1. Torsion should have occurred in a virginal genital tract in order to exclude all possibilities of venereal infection and the mechanical derangements following pregnancy.
2. In uncertain cases of virginity the age should be limited to the beginning of puberty (from 13 to 14 years).
3. The ovary and the adnexa on the opposite side should not show any gross pathologic process on operative inspection.

34. Chastenet de Géry and Lacroix: Torsion des deux trompes en apparence normales et histologiquement tuberculeuses, *Bull. et mém. Soc. nat. de chir.* **53**: 558-561, 1927.

35. Askey, E. V.: Hydrosalpinx—with Torsion of Pedicle: Report of Case, *California & West. Med.* **37**:252-254, 1932.

4. A careful histologic examination must have been done. It should not reveal any evidence of inflammation, neoplasm or pregnancy.

5. In case of torsion on the right side the histologic examination of the removed appendix should not show periappendicitis to any marked degree.

In spite of our criticism of so many reports on torsion of the undiseased fallopian tube, we feel forced by the accumulated material to admit its possible occurrence. But the more precise reports would probably throw a little more light on the still obscure etiology and mechanism of this accident. There exists a rather extensive discussion in the literature on the etiology of torsion, and we refer the reader to these papers for more detailed information (Schweitzer,⁹ Darner,¹⁶ Gabe,¹³ Koster,¹⁷ Terruhn,³⁶ Saitz,³⁷ Shute²⁶ and others).

We present only briefly the advanced theories:

1. The hemodynamic theory. This theory, the oldest and most discussed one for explanation of torsion of intra-abdominal organs, was advanced by Payr.³⁸ It was applied by Schweitzer and other authors for an explanation of torsion of the normal fallopian tube. The essential fact in this theory is that the veins of the mesosalpinx are longer and more flexible than the arteries, and in cases of venous congestion they assume a spiral course, which favors torsion. In fact, it was possible to produce torsion artificially in such a manner. This theory is well fit to explain the numerous cases of torsion during pregnancy or in connection with menstruation. The literature reveals over twenty-five reports with an obvious connection of the torsion with the menses.

2. Sellheim's theory. Sellheim³⁹ advanced the theory of the transformation of the movements of the body on the internal organs. Sudden changes or stoppage of certain movements may produce torsion.

3. The anatomic theory. According to this theory, any malformation in the mesosalpinx or the anatomic structure of the tube favors torsion. The most frequent finding is an abnormally long mesosalpinx. Gengebach⁴⁰ found it in all of his six cases. Other factors also, such as acces-

36. Terruhn, E.: Zur Genese der Haematosalpinx unter der Berücksichtigung der Torsion, *Ztschr. f. Geburtsh. u. Gynäk.* **92**:432-449, 1927.

37. Saitz, O.: Zur Aetiologie der spontanen Tubentorsion, *Zentralbl. f. Gynäk.* **55**:222-224, 1931.

38. Payr, E.: Weitere experimentelle und klinische Beiträge zur Frage der Stieldrehung intraperitonealer Organe und Geschwülste, *Deutsche Ztschr. f. Chir.* **85**:392-451, 1906.

39. Sellheim, H.: Erklärung der Achsendrehung innerer Organe, sowie der Drehung, Umschlingung und Verknotung der Nabelschnur, *München. med. Wehnschr.* **69**:1237-1239, 1922.

40. Gengebach, A.: Sechs Fälle von Tubentorsion, *Ztschr. f. Geburtsh. u. Gynäk.* **97**:476-486, 1930.

sory ostia, hydatids of Morgagni, changes in the length and thickness of the tube and, last but not least, the persistence of spiral winding, may be of etiologic importance. Some postmortem observations on still-born and new-born infants led us to believe that the persistence of the fetal tortuosity needs a more serious consideration in the etiology of the spontaneous torsion. Our observations correspond to those of Shute.

4. The physiologic theory. Recently, new physiologic factors were advanced for the explanation of torsion. It is a well known fact that the human tube as well as that of many animals undergoes varying physiologic contractions (Corner,⁴¹ von Mickulicz-Radecki,⁴² Mauclore⁴³ and others). Disturbances of these regular peristaltic movements, such as spasm and other dysfunctions, are believed to be important etiologic factors (Darner¹⁶ and Regad²⁷).

5. The theory of the importance of a vulvovaginitis in childhood, genital complications of the acute exanthemas and attenuated tuberculosis. These factors have been emphasized by Anspach³ and Norris⁶ and recently by Thorek.¹⁴ These diseases may have produced an unrecognized hydrosalpinx, thus creating a cystic structure. In contradiction to a general acceptance of this opinion, such as disease as gonorrhea, measles, scarlet fever or tuberculosis would probably have had a bilateral effect on the tubes, if any. Furthermore, in some reports we find the statement that the fimbriated end of the oviduct was open and the fimbriae were normal in appearance.

6. The traumatic theory. Five cases are reported in the literature in which the torsion followed an accident or trauma (Rueder,²⁹ Laemmle,⁴⁴ Koehler,⁴⁵ Cottalorda,⁴⁶ Charbonnier and Brandt⁴⁷). If only *post hoc* and not *propter hoc*—we do not claim to decide it.

7. The theory of the influence of certain drugs. This factor must be considered. In the case reported by Caraven¹¹ torsion occurred after an application of apiol (parsley camphor; the dimethylmethylene ester of allyltetroxybenzene).

41. Corner, G. W.: Cyclic Variation in Uterine and Tubal Contraction Waves. *Am. J. Anat.* **32**:345-351, 1923.

42. von Mikulicz-Radecki, F.: Zur Physiologie der Tube. Experimentelle Studien ueber die Spontanbewegungen der Kaninchentube in situ, *Zentralbl. f. Gynäk.* **49**:1655-1662, 1925.

43. Mauclore: A propos de la torsion de la trompe utérine, *Bull. et mém. Soc. nat. de chir.* **53**:583, 1927.

44. Laemmle, K.: Ein weiterer Beitrag zur Frage der Eileiterdrehung, *Zentralbl. f. Gynäk.* **47**:436, 1923.

45. Koehler, M.: Torsion normaler Adnexe bei Enteroptose, *Wien. klin. Wchnschr.* **40**:1387-1388, 1927.

46. Cottalorda, J.: Torsion de la trompe saine en relation possible avec un traumatisme, *Bull. Soc. d'obst. et de gynec.* **21**:551-553, 1932.

47. Charbonnier, A., and Brandt, H.: Un cas de torsion traumatique des annexes saines, *Bull. et mém. Soc. nat. de chir.* **61**:835-837, 1935.

As to the marked predominance of torsion on the right side, the following factors have been brought out to explain it: (*a*) the presence of the sigmoid colon on the left side, (*b*) the peristaltis of the small intestines on the right, (*c*) the spastic contractions of the cecum on the right and (*d*) the nearness of the appendix on the right.

If we try to apply any of the etiologic factors for an explanation of the case we are reporting, we shall find ourselves in difficulty. Torsion occurred before the onset of menstruation, there was no evidence of vulvovaginitis, the acute exanthemas were particularly mild, no abnormally long mesosalpinx was noted and no trauma occurred in connection with the torsion. In fact, the etiology in our case appears rather obscure and open only to pure theoretical speculations.

DIAGNOSIS

The acute forms of torsion are characterized by a sudden attack of severe pains in the iliac fossa, with rapid pulse and progressive agitation. The fever is mostly moderate and in no proportion to the rapidity of the pulse. This is considered an important differential diagnostic sign. The fever, leukocytosis and occasional presence of albuminuria result most probably from the absorption of toxins from the necrotic tube. Sometimes prodromal symptoms are present and are characterized by moderate pains in the iliac fossa during or at the time of menstruation. The established clinical picture is dominated by various functional disturbances. The pain is mostly marked. Muscular spasm is present in about 70 per cent of cases of torsion of the undiseased tube. Of the digestive troubles, vomiting is frequent (80 per cent), often being biliary in character. Later, an obstinate constipation frequently results. Urinary troubles, such as retention of urine and dysuria, are also rather frequent. Metrorrhagia is less common.

The frequency with which the symptoms of tubal torsion simulate a lesion of the appendix makes this mistake in diagnosis a frequent one. A careful rectal examination should be of value. The conditions involved in the differential diagnosis include, further: ovarian cyst with a twisted pedicle, rupture of a corpus luteum hematoma, biliary or renal colic, perforation of the intestine, intestinal obstruction, salpingitis and ectopic pregnancy.

Some of the French authors claim to have correctly diagnosed torsion of the tube clinically before operation. They have even described a syndrome of tubal torsion (Regad²⁷). It is said to consist of the following signs: (1) a severe attack of pelvic pains, with agitation and anguish, appearing in the course of or in evident connection with menstruation; (2) rapid pulse coexisting with a nearly normal temperature; (3) the

presence of a palpable mass lateral to the uterus, of irregular consistency, mobile and extremely tender to touch, and (4) absence of any signs pathognomonic of tubal pregnancy.

In any case, torsion of the fallopian tube is now an established clinical and pathologic entity and must be thought of in all obscure abdominal accidents.

SUMMARY

A case of isolated torsion of the fallopian tube in a girl 10½ years old is reported, and the literature is reviewed.

Only three similar cases of tubal torsion in girls who have not yet menstruated have been reported previously. This case thus becomes the fourth on record.

A critical analysis of the reports on torsion of a normal tube reveals that many lack proof that the organ was undiseased before torsion.

The histologic examination is the most important criterion for the normality of the twisted tube. The difficulty of an exact determination whether or not the tube was undiseased before torsion is emphasized and illustrated in the reported case.

A sharp distinction is made between the tube of a virgin and that of a married woman. Reports of authentic cases of torsion of the normal virginal tube are collected from the world literature, and the data are tabulated.

Some suggestions are made as to how to determine authentic cases of torsion of normal tubes.

The etiology is briefly discussed, and the existing theories are presented. The etiology in the reported case is rather obscure.

EXPERIMENTAL STUDIES ON LYMPHATIC BLOCKAGE

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The fact that complete blockage of the lymphatic system has never been produced experimentally is testimony of the difficulty of causing such a condition. The explanation of this remarkable fact must lie in the capacity for the development of a collateral circulation. A multiple origin of the lymphatics from the veins was shown by Sabin.¹ She stated: "In the pig the lymphatics bud off from the veins in two places, from the anterior cardinal veins and from the veins of the Wolffian body. There are two sets of paired sacs, the jugular and the iliac; and two unpaired sacs, the retroperitoneal and the cisterna chyli." Later investigations by Clark and Clark² demonstrated that in the early stages of development of the chick there are numerous connections between the earliest lymphatics and the blood vessels. The complete picture concerning these anastomoses has not been determined, nor has it been established what proportion of these vessels remain capable of developing functional patency in adult life. Many investigators have found anastomoses between lymphatic vessels and veins, but the adequacy of the valves has made retrograde injection so difficult that such surveys are always incomplete.³

The maintenance of drainage through the thoracic duct has by many investigators been considered essential to life. Others have questioned the soundness of this theorem and have based their conclusions on

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1. Sabin, Florence R.: *The Origin and Development of the Lymphatic System*, Baltimore, Johns Hopkins Press, 1913.

2. Clark, Eliot R., and Clark, Eleanor L.: *Contrib. Embryol.* 9:449, 1920.

3. Job, T. T.: *Am. J. Anat.* 24:467, 1918.

numerous experiments in which the duct itself has been blocked or obliterated. On the other hand, these arguments are obviously worthless, since it has been demonstrated that there is a widespread network of anastomosing vessels between the lymphatics and the veins, and hence negative experiments are meaningless. Not only has this condition made impossible the determination of the extent to which the lymphatic system is essential to the life of the organism, but it has rendered difficult the analysis of the physiologic significance of the system in part and as a whole. Furthermore, in regard to localized areas, the enormous regenerative capacity possessed by lymphatics (Reichert⁴) has made an analysis of their local importance extraordinarily difficult.

In approaching the study of lymphatic drainage and in planning experiments for the elimination of this drainage, the principal objectives were to answer these queries: 1. Is the integrity of the lymphatic system necessary to life? 2. What effect does elimination or blockage of the lymphatic system have on the supply of leukocytes to the circulating blood? 3. What effect does this blockage have on the nutrition of the animal and, in particular, on the absorption and utilization of fats? The present series of experiments has been projected in an effort to answer these three questions. Information has been obtained which illuminates them to some extent, but much more elaborate studies will be necessary before a final answer can be obtained concerning the basic physiology of the lymphatic system.

In considering the first of these questions, it may be stated that no definite proof is available from previous studies as to whether or not the integrity of the lymphatic system is essential to life. This is due simply to the fact that there has never been any certain demonstration of complete blockage. It is known that man and experimental animals tolerate occlusion of the thoracic duct. On the other hand, a fistula of the thoracic duct is usually associated with a loss in weight and death.

In considering the alterations in the cellular picture of the blood, it is important to consider the observations of Lee.⁵ After ligation of the thoracic duct in the chest, an immediate decrease in the lymphocytes to 56 per cent of the original level was noted, the count returning to normal in the third week. This return to normal was believed by Lee to result from the establishment of a collateral lymphatic circulation.

The present situation as regards the studies on the cellular composition of the blood after obstruction of the lymphatics is summarized by Drinker and Field⁶ as follows: "No experiments are available in

4. Reichert, Frederick Lect: The Regeneration of the Lymphatics, *Arch. Surg.* **13**:871 (Dec.) 1926.

5. Lee, Ferdinand C.: *J. Exper. Med.* **36**:247, 1922.

6. Drinker, Cecil K., and Field, Madeleine E.: *Lymphatics, Lymph and Tissue Fluid*, Baltimore, Williams & Wilkins Company, 1933.

which all the lymphatic entrances on the left and right sides have been either ligated or exteriorized, and without such experiments we can have but an idea of the effects of lymph blockage on the cellular composition of the blood." The literature on the cellular composition of the lymph from the thoracic duct has been reviewed by Drinker and Field and need not be repeated here in detail. After a consideration of the studies of the lymph from the thoracic duct, as well as of the experiments of Lee, it is obvious that the inflow of lymph into the vascular system from the thoracic duct must be of considerable importance in determining the relative percentages of lymphocytes present in the circulating blood.

The third point of interest in relation to blockage of the lymphatics has to do with the possibility of producing nutritional disturbances by preventing the entrance of fat into the blood stream. The fact that lymph may enter the subclavian veins through the right lymphatic duct has not been taken into consideration in most of the work. Drinker and Field stated: "The problem of nutritional disturbances and survival after excluding the lymph from the circulation seems never to have been attacked with much success, not because the thoracic duct has not been tied but because failure to tie the entrances on the right side or else the onset of infection have vitiated the results." Bloor⁷ stated that 60 per cent of the absorbed fat is the largest amount that has been recovered from the thoracic duct. Perhaps the most significant work on the relationship of lymphatic obstruction and nutritional disturbances is that of Schmidt-Mülheim.⁸ He divided the left lymphatic, or thoracic, duct and the right lymphatic duct and ligated the veins in the lower part of the neck into which the ducts enter. No nutritional disturbances were observed in the animals, and he found that the lymphatic apparatus was not necessary for the passage of the products of protein digestion into the blood stream. Lee⁹ found no evidence of nutritional disturbances in cats which were observed for as long as seventy-seven days after the occlusion of the thoracic duct. In summary, the evidence to date indicates that patency of the thoracic duct is not essential. However, attempts to block the entrance of lymph into the circulation have not been successful.

Our interest in the present problem was aroused by the results of experiments¹⁰ on dogs and cats in which the superior vena cava was ligated. Chyllothorax resulted from this procedure in approximately 50 per cent of the animals. It seems likely that the accumulation of chyle

7. Bloor, W. R.: *Physiol. Rev.* **2**:92, 1922.

8. Schmidt-Mülheim, Adolf: *Arch. f. Anat. u. Physiol. (Physiol. Abt.)*, 1877, p. 549.

9. Lee, Ferdinand C.: *Bull. Johns Hopkins Hosp.* **33**:21, 1922.

10. Blalock, Alfred; Cunningham, R. S., and Robinson, C. S.: *Ann. Surg.* **104**:359 (Sept.) 1936.

in the chest after ligation of the superior vena cava is due to interference with the normal emptying of the lymphatic ducts into the tributaries of this vein as a result of the high venous pressure. Most of the animals remained in good condition if the chyle was aspirated frequently from the chest in order to prevent too great a reduction in the vital capacity. After varying intervals of time, the reaccumulation of chyle in the pleural cavities ceased. This was thought to bear a relationship to the decline in venous pressure as the collateral veins increased in size. An analysis of the condition which ensued after occlusion of the superior vena cava was complicated by the fact that one could not separate with certainty the effects of venous obstruction alone from those effects due to the impediment to the flow of lymph. Since occlusion of the superior vena cava cannot be produced without causing an increase in the pressure in the lymphatics which drain into it, it was decided that an attempt should be made to block the lymphatics themselves without causing an associated venous obstruction. It was with this idea in mind that the experiments reported here were begun. They have been extended to include studies on the cellular composition of the blood before and after occlusion of various lymphatic vessels. In addition, the state of nutrition of the animals has been observed, and an attempt has been made to determine whether or not patency of the lymphatic system is essential to life. A few studies, as yet incomplete, have been performed in which the fat in the blood was determined repeatedly after the feeding of cream by stomach tube.

METHODS

Dogs were used as the experimental animals in some instances and cats in others. All of the operations were performed with the animal under general anesthesia, inhalation ether being used in some experiments and pentobarbital sodium, administered intravenously, being employed in others. Various operative procedures were carried out in the attempts to produce complete blockage of the lymphatic system. A total of two hundred and sixty-seven operations were performed on fifty-two dogs and twenty-two cats, or an average of almost four operations per animal. The greatest number of operations on a single subject was seven. The operative procedures were not spaced at regular intervals. It was believed at the beginning of the work that the greatest likelihood of producing lymphatic obstruction would be found in chronic experiments in which infrequent operations were performed and in which the animals were observed for long periods. Later, when it became evident that this procedure had failed to produce obstruction, it was decided that the best possibility rested in the causing of massive obstruction of the lymphatic system without allowing sufficient time for the development of large collateral lymph vessels. The order of the operative procedures also varied in the different experiments. In some instances the initial operative attack was on the large ducts at the entrances into the veins of the neck. In other experiments attempts were made first to block the lymphatics nearer the points of origin and subsequently to occlude the lymphatic ducts.

A brief description of the various operative procedures follows. These procedures include: 1. Ligation and division of the thoracic duct in the neck. An

incision was made over the left external jugular vein in the lower third of the neck, and the tissues were freed from the proximal portion of the vein. The danger of entering the pleural cavity was minimized by adhering closely to the wall of the vein in the dissection. The thoracic duct could be found without difficulty, and it was doubly ligated and divided. In addition, any other ducts which were seen were ligated. 2. Ligation and division of the lymphatic duct on the right side of the neck. The duct was exposed in much the same way as the thoracic duct. An incision was made over the proximal part of the external jugular vein, and the junction of the jugular and the axillary vein was exposed. Usually, the lymph vessels could be seen; and when noted they were ligated and divided. 3. Intrathoracic occlusion of the thoracic duct. This operation is an extension of that described by Lec.⁹ An intercostal transpleural incision was made at the level of the eighth thoracic vertebra. The surrounding tissues were separated from the wall of the aorta. These tissues, together with the thoracic duct and the azygos vein, were doubly ligated. Sodium morrhuate was injected through an incision in the left flank, although an approach on the right was used in a few experiments. The cisterna was visualized as it lies just posterior to the abdominal aorta. Sodium morrhuate was injected into the cisterna, and it was dissected away from the aorta as completely as possible. An attempt was made to ligate some of the lymphatics which entered the cisterna. Several cubic centimeters of sodium morrhuate was left at the site from which the cisterna had been removed. 5. Attacks on the lymphatics and lymph nodes in the peritoneal cavity. These procedures were numerous and varied. In some experiments all of these were carried out, while in others only one or more were used. One of these procedures consisted of the injection of sodium morrhuate (Searle) or quinine and urea hydrochloride (usually the former) into the mesenteric lymphatics. A small needle was introduced into these lymphatics a short distance from the wall of the intestine, and the solution was injected. As many of the mesenteric lymphatics as possible were treated in this manner. In some experiments the injection of the sclerosing solution was followed by the introduction of crystalline silica (Drinker). Another procedure consisted of the injection of one of the sclerosing solutions into the larger lymph vessels which lie just behind the posterior peritoneum and to either side of the vertebral column. These vessels were quite prominent in the animals in which the large trunks in the chest had been occluded. This was particularly true of the lymph vessels in the neighborhood of the junction of the renal veins and the inferior vena cava. In some instances a number of these lymph vessels were ligated. Still another procedure consisted of the injection of sclerosing solutions directly into the lymph nodes. A needle was inserted into the substance of the various glands, and the solution was introduced slowly. As has been stated, the order of the operations varied in the different experiments. In a few of these as many as three of the procedures were performed on the same day. This was done with the idea of producing as massive an obstruction as possible. The quantity of the sclerosing solutions which can be injected without causing death was the limiting factor in the extent of the procedures that were carried out in the peritoneal cavity. It was found not to be safe to introduce more than 15 cc. of the sodium morrhuate at one operation into a dog weighing 10 Kg.

In the majority of the animals studied, blood counts were made several days preceding the first operation and were continued for periods varying from a few weeks to several months, usually at biweekly or triweekly intervals. Total white blood cell counts were made in the usual manner. The differential counts were done on coverslip preparations stained with Wright's stain. At the time the blood was taken several pairs of coverslips were pulled, and the best pair was selected; both coverslips were stained, and 200 or 400 cells were counted on each. As was pointed out by Sabin, Cunningham, Doan and Kindwall,¹¹ more accurate results are obtained by this method than by counting the same number of cells on a single coverslip. It has been our routine to count 200 cells on each coverslip when the total counts were under 20,000, and 400 cells when they were above 20,000. The technical difficulties involved in studying so large a series of animals with the supravital method made its use in these experiments impossible. While qualitative changes undoubtedly must exist in these cells, our objective at the moment was to utilize the blood more as a control for the effect of the operative procedures than to examine any qualitative effects of the operative procedures on the cells of the blood. This will, however, be taken into consideration in further experiments.

The superior vena cava was ligated in a few of the experiments. This was usually done toward the end of the observation period and when the effects of the lymphatic blockage, as reflected in the cellular picture of the blood, had disappeared.

As has been stated, the cellular composition of the blood was determined frequently in most of the experiments, and the animals were observed for varying intervals of time. In some instances the period of observation was terminated by the spontaneous death of the animals; in others, death was caused painlessly when the appearance of the animal and the cellular picture of the blood indicated that death was imminent. In still others (and these constituted the majority of the experiments) the animals were killed while still in good condition, and careful autopsies were performed. The autopsies included a careful search for lymphaticovenous communications. This search was carried out most successfully by bleeding the animals almost to the point of death and then washing out the greater part of the remaining blood by the introduction of salt solution under pressure into the circulation. Immediately after death, a solution of berlin blue was injected into the lymphatics, and a search was made for communications between the lymphatics and the veins. The removal of the red blood cells greatly facilitated the search.

RESULTS

Fifty-two dogs and twenty-two cats were used in these studies. A variety of operations have been performed, but, in general, these have consisted of blocking the lymphatic ducts in the neck and chest, of destroying the cisterna and of interfering with the drainage of the mesenteric lymphatics. The animals were studied over periods ranging from a few days to several months; hence complete uniformity of results was not obtained. In many of the animals there was undoubtedly temporary obstruction, which was relieved by the opening of the

11. Sabin, F. R.; Cunningham, R. S.; Doan, C. A., and Kindwall, J. A.: *Bull. Johns Hopkins Hosp.* 37:14, 1925.

collateral lymph channels, and in these animals there was a marked temporary change in the blood picture, with a return to normal. There were many examples of this sort. For example, in dog 34 there was obviously marked obstruction after ligation of the ducts and destruction of the cisterna. The lymphocyte count fell from 2,318 to 787 cells and the eosinophil count, from 688 to 164. At autopsy, however, communications with the inferior vena cava were demonstrated, and prior to autopsy the number of both the lymphocytes and the eosinophils had.

TABLE 1.—*Data on Animals with Complete Obstruction*

Dog No.	Group No. (table 5)	Comment
15	I	Mesenteric lymphatics appeared as large white cords; no L-V* communications
28	I	All lymphatics in abdominal viscera tremendously dilated with chyle; no L-V communications
121	VII	Mesenteric lymphatics appeared as large white cords in many areas; no L-V communications

* Lymphaticovenous.

TABLE 2.—*Data on Animals with Marked Obstruction*

Dog No.	Group No. (table 5)	Comment
2	VII	Chyle extravasated into mesentery; mesenteric lymphatics dilated; lymph nodes enlarged; no L-V* communications
3	I	Marked distention of lower abdominal lymphatics; no L-V communications
13	III	Marked obstruction of mesenteric lymphatics; no L-V communications
41	II	Generalized retrograde injections; small amount of extravasated chyle in mesentery; small duodenal ulcer; no L-V communications
108	VII	Mesenteric lymphatics appeared as large white cords; generalized retrograde injection; no L-V communications
114	II	Marked obstruction of mesenteric lymphatics (ileum); no L-V communications

* Lymphaticovenous.

increased, although the averages had not returned to the preoperative level.

Before the alterations in the cellular composition of the blood were considered, the data in regard to lymphaticovenous communications as shown at autopsy will be enumerated. In nine experiments a careful search did not reveal such connections. The obstruction was complete in three of these, and the data are enumerated in table 1. These experiments will be described in detail. There was evidence of marked blockage in the remaining six experiments, and the data are contained in table 2. There were eleven animals which showed partial obstruction and in which communications were demonstrated with veins other than the normal connections which had been destroyed at operation. In most

instances these connections included anastomoses with the vena cava. In some of these animals temporary blockage occurred, but in none of them was the blockage maintained to a fatal termination or to an extensive degree. The data are enumerated in table 3.

In the study of the cellular picture of the blood the lymphocytes were looked on as the principal indication of changes in the blood cells; changes in other cells have been, as far as possible, related to changes in the lymphocytes. This method of approach was taken because it has been shown by many observers that there are large numbers of lymphocytes in the lymph from the thoracic duct. Rous¹² found that these cells

TABLE 3.—*Data on Animals with Partial Obstruction*

Dog No.	Group No. (table 5)	Comment
7	VII	Dilated lymphatics in anterior mediastinum, over surface of pericardium and on surface of large intestine; L-V* communications with inferior vena cava
14	I	Plexus of distended vessels under trachea; L-V communications with axillary vein
17	IV	Regional obstruction of intestinal lymphatics; lymphatics of omentum prominent; L-V communications with inferior vena cava
22	I	Regional obstruction of intestinal lymphatics; L-V communications with inferior vena cava
23	IV	Regional obstruction of mesenteric lymphatics; L-V communications with inferior vena cava and lumbar vein
29	II	Duodenal lymphatics prominent; L-V collaterals possibly above diaphragm
30	I	Regional mesenteric blockage; L-V communications with inferior vena cava and lumbar vein
44	V	Regional mesenteric blockage; L-V communications with inferior vena cava and mesenteric vein
46	VI	Regional blockage of intestinal lymphatics; L-V communications with vena cava and lumbar vein
72	VII	Generalized retrograde injection; L-V communications questionable
101	VII	Lymph nodes seminecrotic; some clotted material in lymphatics

* Lymphaticovenous.

constituted from 69.8 to 96.8 per cent of the total number of white cells, with an average of 87.6 per cent. According to counts of Bunting and Huston,¹³ there are more lymphocytes poured into the circulation in twenty-four hours than there are total numbers of lymphocytes in the circulating blood at any time.

In general, the plan of approach was to take several preoperative counts, to determine the general level of cells in these animals and then to follow them at regular intervals, usually two or three times a week thereafter. Such a procedure made possible the determining of a continuous curve from the beginning of the experiment to its cessation. Some of these lasted only a few days, and others, several months. To

12. Rous, F. Peyton: *J. Exper. Med.* 10:537, 1908.

13. Bunting, C. H., and Huston, John: *J. Exper. Med.* 33:593, 1921.

analyze these experiments with any degree of objective value has been difficult, since recovery by the development of collateral circulation has been the rule, and hence the evaluation of each operation has been necessarily a part of the curve.

We have attempted to analyze all of the experiments done in terms of changes in the blood, regardless of whether or not permanent blockage occurred, as we felt it important to discover the effect of temporary as well as permanent blockage on the cells of the blood. A brief summary of the results is given in table 4.

The total number of dogs for which blood counts were made was forty-four. These animals have been arranged in seven groups, as shown in table 5. Groups I and II, as will be noted, differ only in that the dogs in group II showed no change in monocytes, while those in group I showed

TABLE 4.—*Summary of Blood Studies in Dogs*

Changes in Blood Picture	No. of Dogs Studied		
	With Preliminary Counts	Without Preliminary Counts*	Total
1. Decrease in lymphocytes.....	23	6	29
2. Decrease in lymphocytes and eosinophils.....	20	4	24
3. Decrease in lymphocytes and eosinophils with an increase in monocytes	12	3	15
4. Decrease in eosinophils only.....	3	0	3
5. Increase in monocytes only:.....	2	2	4
6. No change in blood picture.....	5	3	8
Total number of dogs studied.....			44

* Since no preliminary counts were made, the averages for normal dogs were used for comparison.

a marked increase. Group VII consists primarily of animals on which no preliminary counts were made; therefore, we could not be certain of an increase or decrease in the cell count after the first operation. Nevertheless, in comparison with the average level in normal animals, it is perfectly obvious that certain of these, such as dog 121, had partial or complete blockage after the operation and hence could be included in the group of animals showing a decrease in lymphocytes and eosinophils. Calculated in this way, it will be noted that twenty-four animals showed a consistent decrease in eosinophils and lymphocytes, and five additional animals (a total of twenty-nine) showed a consistent decrease in lymphocytes alone. While this is not in any sense final proof of a profound association between these two types of cells, it is nevertheless extremely sound evidence that there is some effect on the eosinophils of the circulation after obstruction to the inflow of lymph into the blood stream. In eight of the animals there was no change in the blood picture, and in fifteen animals there was no appreciable decrease in

lymphocytes after any of the operations. These negative results are obviously explicable in terms of an immediately available collateral circulation. With the tremendous development which the collateral circulation is capable of undergoing, it is perfectly obvious that we cannot assume that a failure to obtain a decrease in lymphocytes after ligation of the thoracic duct in any way invalidates the theory of the importance of the lymph supply to the maintenance of lymphocytic inflow into the circulation. Assuming these facts to be true, the experiments carried out here demonstrate, first, that in a large proportion of the animals there is definite evidence of lymphatic blockage in terms of reduced supply of lymphocytes to the circulating blood after obstruction and that in the majority of these animals there is a corresponding diminution in the supply of the eosinophils. An important but less marked change is the increase in the monocytes, which, while present in a considerable number of animals (nineteen,), does not seem to be of quite the same importance as the change in lymphocytes and eosinophils. Nevertheless, since this increase in monocytes occurred in fifteen of the twenty-four animals which showed changes in lymphocytes and eosinophils and in only four animals in which these changes did not occur, it would suggest a possible relationship to be investigated further. The three animals which were considered to have complete blockage (table 5) showed a marked decrease in the lymphocytes and eosinophils, and two of them showed a marked increase in the monocytes.

The results of three experiments in which the evidence for lymphatic blockage was most striking will be described in detail.

Dog 28.—The first operation on dog 28 was performed on May 13, 1935. It consisted of exposing the thoracic duct through a transpleural incision at the level of the eighth dorsal vertebra. It was doubly ligated together with the azygos vein and the tissues surrounding the aorta. Sodium morrhuate was injected into the structures both above and below the ligatures. In addition, the mediastinal pleura and the cardiac ligament were doubly ligated and divided. The incision into the chest was then closed. This procedure was performed under positive pressure intratracheal anesthesia. The second operation was performed on May 24; in fact, three operations were performed on this date. Incisions were made on the right and left sides of the neck, and the lymphatic ducts were ligated and divided. An incision was then made in the left flank, and the cisterna chyli was exposed. The cisterna was filled with solid material which looked like chyle that had clotted. The greater part of the cisterna was removed. Several cubic centimeters of sodium morrhuate was placed in the neighborhood of the aorta, and the incision was closed.

The animal seemed to get along satisfactorily for the following five days, but became quite short of breath on the sixth day, May 30. Both pleural cavities were aspirated at this time, 600 cc. of fluid being obtained from the left side and 250 cc. from the right. The fluid was whitish yellow. After it had stood, a sediment which equaled approximately one fourth of the total volume precipitated out. When shaken, the fluid was flaky. This fluid showed a total count of

120,000 cells per cubic millimeter. Supravital studies showed that these cells were all polymorphonuclear leukocytes, with the exception of an occasional elastomocyte. They were all living cells, but practically every cell contained a peripheral ring of fat droplets.

The following day, May 31, the animal appeared ill, and it was decided to kill him, since death would have occurred almost certainly within twenty-four hours. The respiratory rate was rapid. The eosinophils had disappeared from the blood

TABLE 5.—*Blood Changes in Dogs Selected as Typical of Each Group*

Group*	Lymphocytes	Eosino- phils	Mono- cytes	Group*	Lymphocytes	Eosino- phils	Mono- cytes
Group I (12 animals)				Group IV (3 animals)			
Dog 15†				Dog 47			
Preliminary (5)†.....	3,688	3,145	609	Preliminary (3).....	1,766	2,511	374
1. Duct (11).....	584	191	2,313	1. Thoracic (6).....	1,190	603	1,559
Dog 25†				2. Duct and cisterna			
Preliminary (3).....	1,441	929	877	(6).....	1,182	1,005	1,070
1. Thoracic (5).....	1,262	223	2,656	Recovery (5).....	1,280	1,552	709
2. Duct and cisterna				3. Abdominal (5).....	723	672	952
(2).....	509	0	2,022				
Group II (7 animals)				Group V (2 animals)			
Dog 41#				Dog 101			
Preliminary (4).....	1,001	1,200	919	Preliminary (1).....	400	200	800
1, cava; 2, lymph				1. Cisterna (6).....	642	200	1,465
nodes; 3 cisterna				Recovery (12).....	2,237	730	1,131
(2).....	240	22	931	2. Duct (12).....	1,029	512	1,019
Dog 49							
Preliminary (3).....	2,020	2,010	1,070	Group VI (7 animals)			
1. Thoracic (15).....	561	302	1,101	Dog 46			
Recovery (10).....	1,583	4,100	1,570	Preliminary (3).....	2,040	1,107	2,167
Dog 114#				1. Thoracic (6).....	2,467	991	3,671
Preliminary (1).....	1,524	432	2,688	Recovery (15).....	1,887	1,136	1,778
1. Removal of spleen (1).....	584	265	1,314	2. Duct and cisterna			
2. Thoracic (5).....	467	342	2,378	(7).....	1,351	1,207	2,273
Group III (3 animals)				Group VII (0 animals)			
Dog 107				Dog 108#			
Preliminary (1).....	1,572	736	2,024	2 previous opera-			
1. Abdominal (2).....	400	606	1,085	tions			
2. Chest (3).....	343	230	1,975	Preliminary (3).....	416	99	1,059
3. Abdominal (7).....	565	260	1,538	3. Abdominal (1)...	390	0	2,496
				Dog 121†			
				3 previous opera-			
				tions			
				Preliminary (3).....	883	497	1,777
				4. Abdominal (11)...	359	114	1,125
				5. Thoracic (3).....	262	105	1,888

* The dogs were divided as follows: group I, dogs in which there was a consistent decrease in eosinophils and lymphocytes with an accompanying increase in monocytes; group II, dogs in which there was a consistent decrease in lymphocytes and eosinophils, but with no accompanying change in monocytes; group III, dogs in which there was a decrease in lymphocytes with no consistent change in other cells; group IV, dogs in which there was a decrease in eosinophils with no consistent change in other cells; group V, dogs in which there was an increase in monocytes with no consistent change in other cells; group VI, dogs in which there were no marked changes in the leukocytes, and group VII, miscellaneous.

† This animal showed complete obstruction at autopsy.

‡ This and other numerals in parentheses represent the number of blood counts made, and the counts given are averages of these.

This animal showed marked obstruction at autopsy.

stream, and the lymphocytes were greatly reduced in number. When the peritoneal cavity was opened, the walls of the stomach and of the entire intestinal tract down to the descending colon were observed to be tremendously infiltrated with chyle. This infiltration started in the base of the mesentery and progressed outward to a considerable distance as an almost solid mass of chyle. There were enormous numbers of lymphatics which obviously had ruptured, but there were also many discrete vessels, particularly over the intestinal wall; these vessels were seen to empty into the mass of extravasated chyle (fig. 1A). All lymph nodes were enormously enlarged, and fluid exuded from their surfaces. The lymph vessels leading from the pelvis were either ruptured or so greatly distended that

their walls could not be made out. The omentum showed an extraordinary injection of the lymphatics in which parallel vessels followed each band of fatty tissue throughout the network of the structure. This is shown to some extent in figure 1*B*, but the photograph does not reveal the true degree of the engorgement of these lymphatics. The lymphatics of the gallbladder, pancreas and hepatic pedicle were enormously dilated. Approximately 10 cc. of yellowish, milky fluid was removed from the peritoneal cavity. The enormous distention of the lymphatics is shown in figures 2*A* and *B*, sections taken from the pancreas and omentum, respectively. In figure 2*C* the distended lymphatics of the submucosa and muscular layers of the intestines are shown containing coagulated lymph.

The chest was opened, and 550 cc. of fluid was removed from the right pleural cavity and only a small quantity from the left. The fluid looked like milk to which had been added a slightly yellowish pigment. The pericardial cavity contained 30 cc. of pure white fluid. The anterior mediastinal lymph nodes and tissues were completely infiltrated with this same fluid. Slight pressure caused obvious leakage, and it appeared that it was through this area that fluid obtained egress into the pleural cavities. Block dissection was used, and the tissues were removed from the neck to the lower portion of the colon. These were fixed immediately in a solution of formaldehyde. The posterior wall of the abdomen was examined, and two large lymph nodes were observed on either side of the vertebral column at the level of the sacral crest; these nodes were approximately 3.5 by 2.5 cm. in size.

In figure 3 and table 5 the counts on the peripheral blood of dog 28 are presented. It will be noted that there is a marked decrease in the eosinophils after the first operation but none in the lymphocytes until after the ligation of the lymphatic ducts. The animal became extremely weak and was killed before the lymphocytes had had sufficient time to reach a stabilized count. The eosinophils had disappeared from the blood stream, and the level had been extremely low for four counts previous to their disappearance. There was a marked increase in the total count, which was explained by the increase in neutrophils which accompanied it. The monocytes were definitely but irregularly increased after the first operation and maintained this high level throughout the course of the experiment.

Dog 15.—This animal weighed 11.75 Kg. After preliminary studies of the cellular picture of the blood, operations were performed on March 7, 1935. Incisions were made on both sides of the neck, and the large lymphatic ducts were ligated and divided. An incision was made in the left flank, and the cisterna chyli was exposed. It was distended with fluid. The major portion of the cisterna was dissected away from the aorta and removed. Several cubic centimeters of sodium morrhuate was placed in the neighborhood of the aorta, and the incision was closed.

Twelve days after the operation, 920 cc. of whitish, slightly blood-tinged fluid was aspirated from the chest. The following day 405 cc. of white fluid was removed. On March 21, two weeks after the operation, the weight had declined to 10.25 Kg. During the succeeding four days a total of 785 cc. of fluid that looked like milk was aspirated from the chest. On March 26 the weight of the dog had decreased to 9 Kg., and three days later it was 7.65 Kg. On the latter date the dog had diarrhea. One hundred cubic centimeters of fluid was withdrawn from the chest at that time. On March 30 and April 1 125 cc. of milky, slightly yellowish fluid was removed. The animal appeared to be quite weak on the latter date. No food had been taken for several days, and the animal had ceased to walk around. When seen at 8 o'clock in the evening of April 1, it seemed doubtful if the dog would survive until the following morning. The temperature was 98.8 F., and the



Fig. 1.—*A*, photograph of the duodenum and pancreas of dog 28, showing enormous numbers of lymphatics in each of these structures. *B*, photograph of the omentum of dog 28. The lymphatics are loaded with fat and can be seen as small thin white lines in the fatty areas.

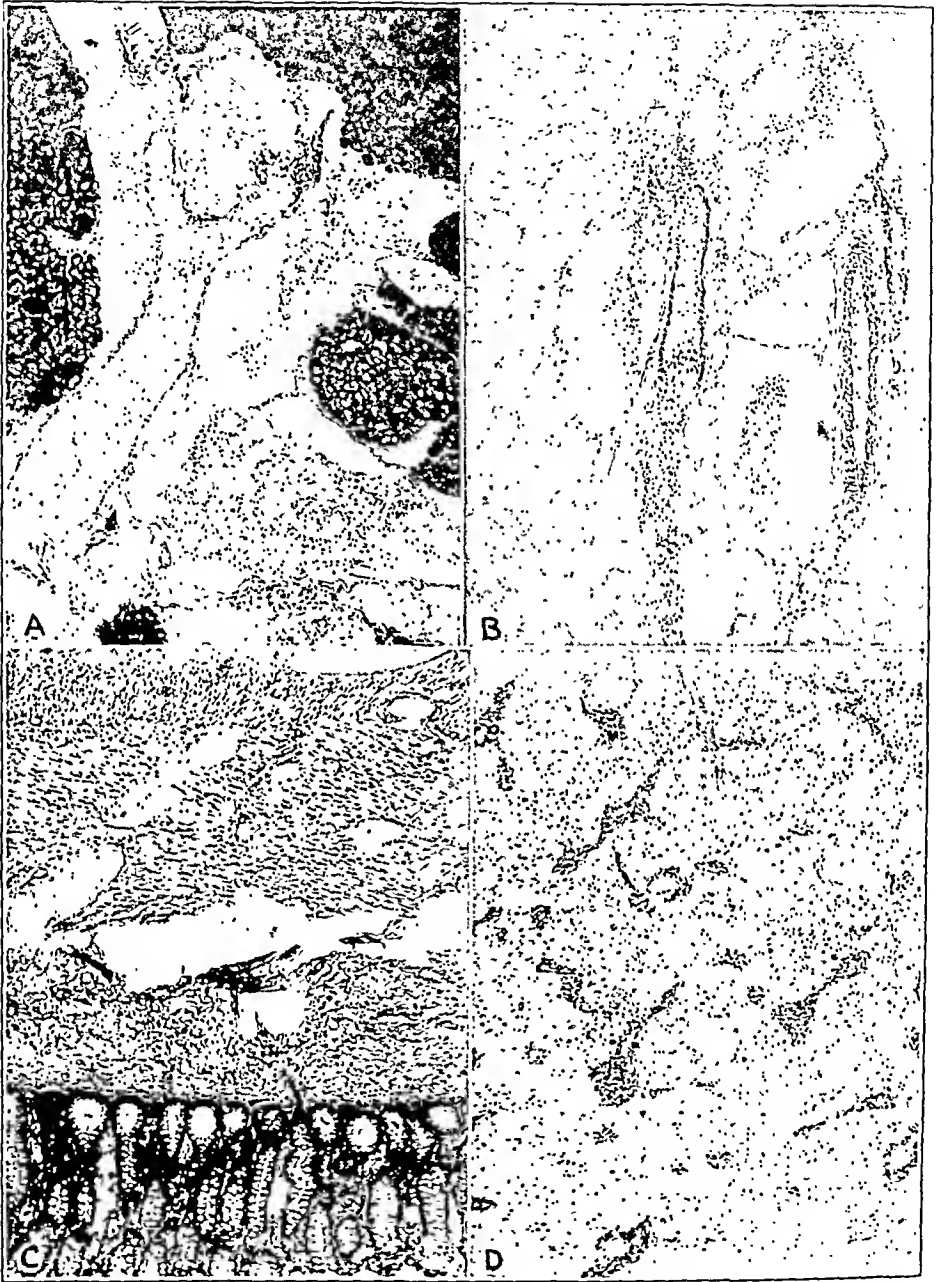


Fig. 2.—*A*, photomicrograph of a section of the pancreas of dog 28, showing enormous distention of the perivascular lymph vessels; $\times 50$. *B*, photomicrograph of a section of the omentum of dog 28, showing marked distention of the lymphatics; $\times 50$. *C*, photomicrograph of a section of the large intestine of dog 28, showing a marked dilatation of the lymphatics in the submucosa and muscularis; $\times 50$. *D*, photomicrograph of a section of the lymph node of dog 15, showing marked dilatation of the central sinus system. The lymphoid tissue is thinned out, depressed and somewhat decreased in amount; $\times 50$.

pulse had a rate of only 98 per minute but was weak. The respiratory rate was not rapid, and the weight was 6.97 Kg. Ether was given by cone, and an abdominal incision was made. The animal died after only a small amount of ether had been administered.

Autopsy showed that most of the mesenteric lymph vessels leading from the small intestine were large white cords which were filled with solid material (fig. 4.4). In the mesentery of the lower part of the ileum several lymphatics were observed which did not contain coagulated material. Berlin blue was injected into these, but the solution did not pass beyond the adjacent lymph node. The lymph nodes were large and edematous. The pleural cavities contained a total of 135 cc. of milky, slightly yellowish fluid. There was no pneumonia. The thoracic duct was

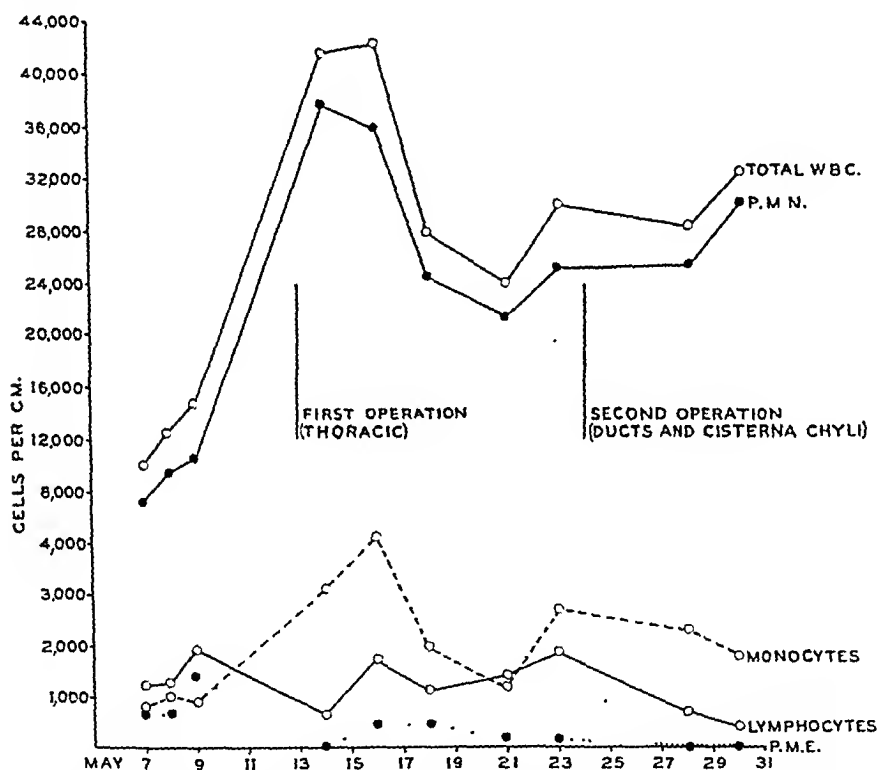


Fig. 3.—Curve showing data on the blood of dog 28. Note particularly the extremely low level of lymphocytes and eosinophils at the end of the experiment.

dilated; it contained coagulated material which could not be expressed. A needle was inserted into the thoracic duct, but fluid could not be forced into the system. The mediastinal lymph nodes were enlarged and edematous.

During the course of the experiment the weight of the animal showed a progressive loss from 11.75 to 6.79 Kg. After the operation on the lymphatic ducts there was a marked change in all the blood elements (fig. 5 and table 5). This change remained fairly constant, though slightly progressive, until the death of the animal. Both the lymphocytes and the eosinophils decreased to an extremely low level; this decrease was slowly progressive until the cells had practically disappeared from the blood stream. The monocytes, while extremely irregular in number, increased to an average of approximately three times the preoperative level, and

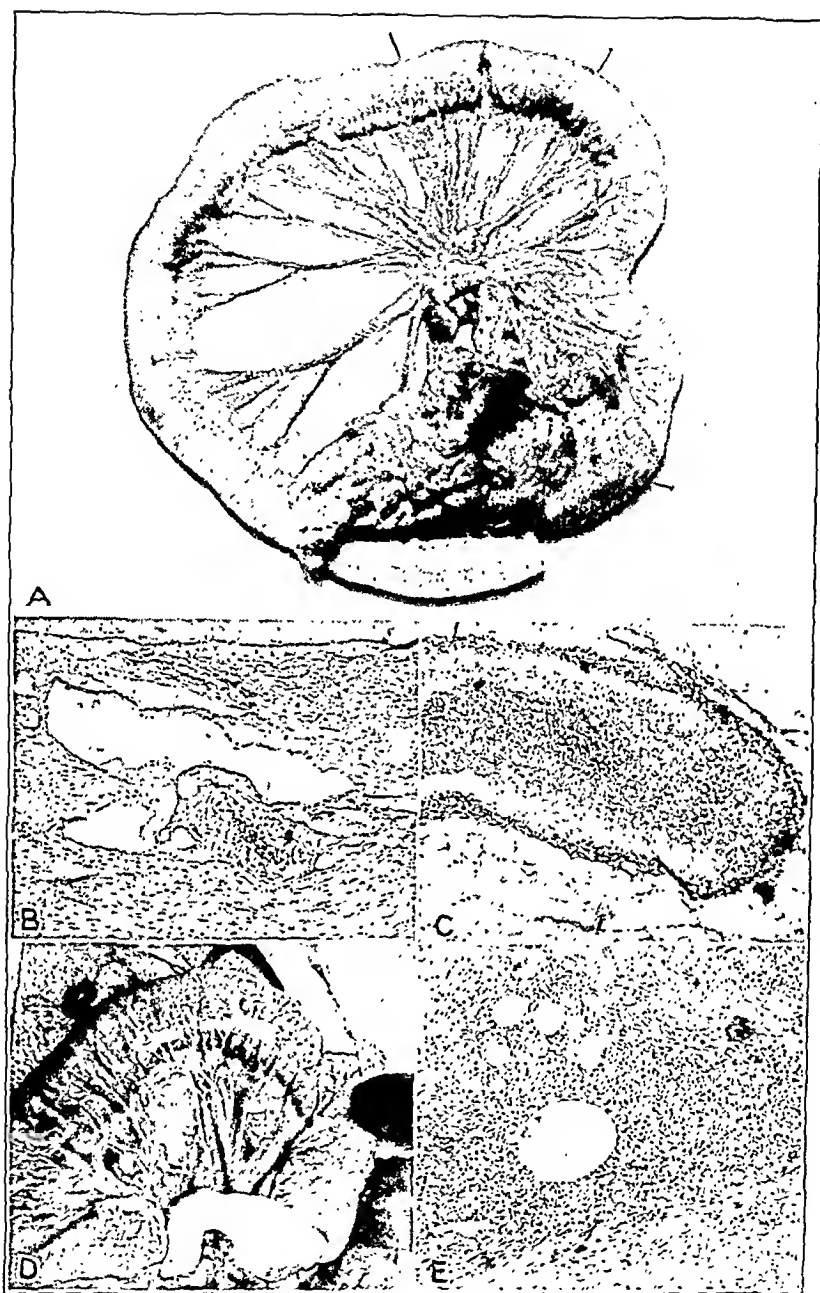


Fig. 4.—*A*, photograph of the small intestine of dog 15, showing mesenteric lymph vessels as large white cords filled with solid material. *B*, photomicrograph of a section of the heart of dog 15, showing distended perivascular lymphatics beneath the epicardium; $\times 50$. *C*, photomicrograph of a section of the mesentery of the small intestine of dog 15, showing the lymphatics distended with coagulated lymph; $\times 50$. *D*, photograph of the small intestine of dog 121, showing the extravasation of chyle into the intestinal wall. *E*, photomicrograph of a section of the lymph nodes of dog 121, showing small residual lymphatics in a mass of reticular tissue; $\times 50$.

at the termination of the experiment were at the highest peak. There was also a marked increase in neutrophils. The correlation between the decrease in lymphocytes and the fall in eosinophils was extremely dramatic in this experiment.

The section in figure 4C was taken from the mesentery of the part of the intestine shown in figure 4A. In this area all of the lymphatics were filled with a coagulum containing cellular debris and a few lymphocytes. In figure 2D is shown a section from a lymph node which was markedly edematous and in which the lymphoid tissue was widely separated, markedly diminished and compressed. In figure 4B is shown tremendously dilated perivascular lymphatics in the cardiac muscle just under the epicardium.

Dog 121.—The operative procedures on dog 121 included a direct attack on the intraperitoneal lymphatics. It should be stated that it is much more difficult

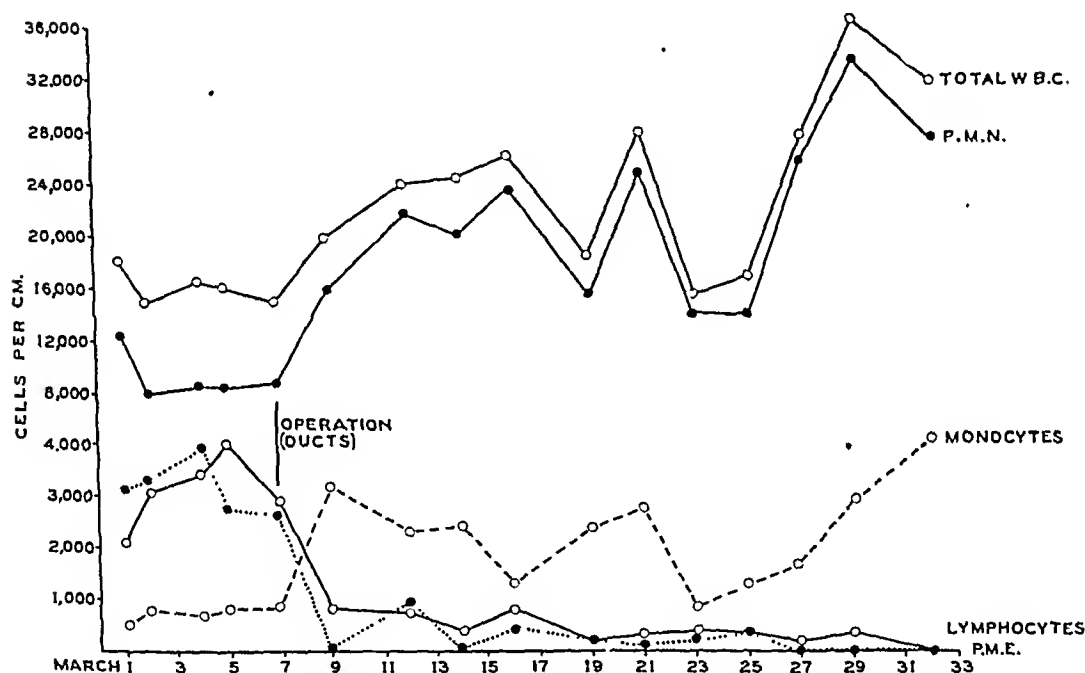


Fig. 5.—Curve showing data on the blood of dog 15. Note particularly the sharp fall in lymphocytes and eosinophils after ligation of the ducts and their progressive diminution to the end of the experiment.

to evaluate the results when such a method is used. This is due in the main to the fact that the manipulation, plus the sclerosing solution, results in numerous adhesions between the various coils of intestines. In the presence of marked blockage of the lymph vessels, the diffuse scarring prevents a striking picture such as that seen in dog 28, in which the lymphatics of the peritoneal cavity had not been attacked directly. The first operation on dog 121 was performed on Sept. 26, 1935. The weight of the dog was 7.4 Kg. Six days later the peritoneal cavity was entered, and 15 cc. of sodium morrhuate was injected into the mesenteric lymphatics and into the lymph vessels in the neighborhood of the inferior vena cava. Three days later, October 5, an incision was made in the left flank, and the cisterna was visualized. The cisterna was filled with coagulated material. It was freed from the surrounding tissues and removed. Free chyle could be seen through

the peritoneum in the abdominal cavity. An opening was made in the peritoneum, and some of the chyle was removed for study. Many dilated lymph vessels which were filled with chyle were seen. Extravasated chyle was noted to be present in the wall of the intestines. The incision in the flank was closed. Three days later, October 8, the animal was given 100 cc. of cream by stomach tube; samples of blood for determination of the fat content were withdrawn at intervals of thirty minutes for six hours. The results will be reported in a later communication.

The weight of the dog on October 10 was 6.77 Kg. The animal appeared to be in good condition. An abdominal incision was made with the animal under ether anesthesia, and the peritoneal cavity was opened. There was an enormous dilatation of the lymph vessels of the intestine which were filled with chyle (fig. 4D). Some

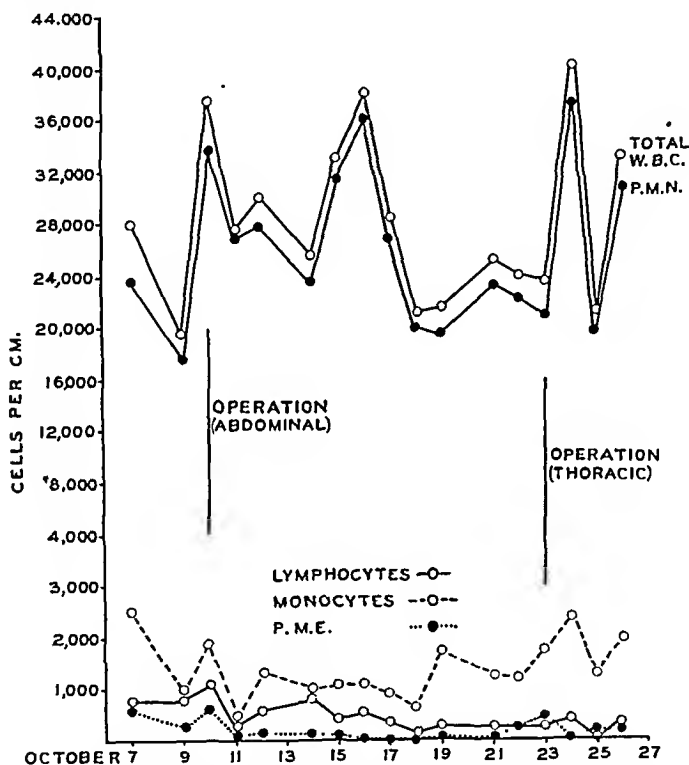


Fig. 6.—Curve showing data on the blood of dog 121. There were no preliminary counts, as three operations had preceded the first shown on the chart. Nevertheless, there was a definite change in lymphocytes and eosinophils following the obstruction of the abdominal lymphatics.

portions of the wall of the intestine were white, due to extravasated chyle. This is shown in figure 4D. Other parts of the intestinal tract could not be visualized owing to the numerous adhesions. Some chyle was extravasated in the omentum, but the alterations were not as marked as those in dog 28. There was a large lymph vessel filled with chyle lying on the anterior surface of the left kidney. Four cubic centimeters of sodium morrhuate was injected into the mesenteric lymph vessels, and 3 cc. was introduced into pelvic lymph nodes. The abdominal incision was closed.

Seven days later, October 17, the weight of the dog was 5.73 Kg. The temperature was 103.4 F., and the pulse rate was 150. The appetite was good. Three days later, the body weight was 5.5 Kg. An incision was made in the lower part of the left side of the chest, and the operation of Lee, plus the division of the mediastinal pleura, was carried out. On October 26 the dog appeared to be ill. The temperature was 103.5 F., the pulse rate 150 and the weight 5.44 Kg. Aspiration of the chest yielded 70 cc. of blood-tinged fluid. The dog had a soft stool, which was very light in color.

No preliminary blood counts were made on dog 121, but the counts made on October 7, which was two days after the third operation, showed an extremely low level both in lymphocytes and in eosinophils (fig. 6). During the next three weeks there was a slowly progressive decrease in the lymphocytes, the eosinophils remain-

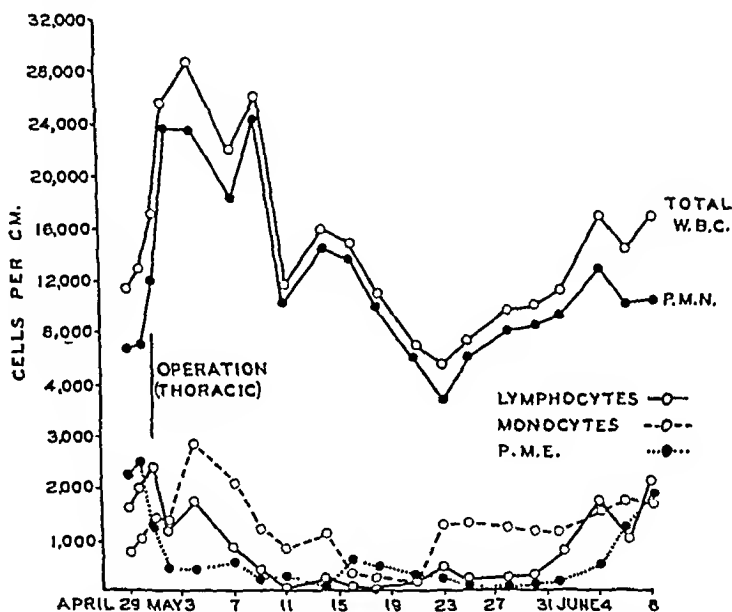


Fig. 7.—Curve showing data on the blood of dog 49. The fall in lymphocytes and eosinophils after the thoracic operation indicates obstruction, while the return to normal indicates the development of collateral circulation.

ing at a low level and being occasionally absent from the blood stream. There was a slow but progressive increase in the monocytes which, however, never reached an extremely high level. The fourth and fifth operations (as shown in figure 6 and table 5) apparently produced slight exacerbations in the slowly progressing change in the eosinophils and lymphocytes.

On October 26 it was believed that the animal would live less than twenty-four hours, and it was therefore killed. Most of the mesenteric lymphatics seen were hard white cords, but others could not be visualized, owing to the diffuse scarring and adhesions. The blood was removed from the vessels by means of a cannula, salt solution being used to wash out the vessels. After this, berlin blue was injected into the mesenteric lymphatics. There was retrograde injection everywhere. No communications between the lymphatics and the veins were demonstrated by the injection of berlin blue, although a careful search was made for such openings.

In several of the other dogs the results were similar to those of the experiment last described (dog 121), but in none of them was the picture as striking as that in dog 28. There was evidence of some regional blockage of the mesenteric lymphatics in most of the experiments in which the procedures were carried out in the peritoneal cavity, but in most instances it was not complete. It was observed frequently that berlin blue would flow in the reverse of the usual direction when introduced into the mesenteric lymphatics.

The sodium morrhuate in some instances caused marked necrosis of lymph nodes. When the nodes were examined a considerable time after the injection of the sclerosing solution, they were extremely hard. The section in figure 4E is from a lymph node in which the effects of the sclerosing solution were relatively complete. A large amount of scar tissue was present, and the peripheral sinuses were almost entirely obliterated. It is extremely interesting to note that lymph channels remained open in many of these nodes. This observation may well account to some extent for the extreme difficulty encountered in obtaining complete blockage in lymph nodes by the introduction of sclerosing solutions. These alterations are in marked contrast to those observed in the experiments in which blockage was obtained without the direct attack on the intraperitoneal lymphatics and hence without the injection of sodium morrhuate into these vessels. In these studies the lymph nodes were markedly enlarged and edematous. No scarring was present. The lymph sinuses were scanty and widely separated by lakes of fluid (fig. 2D).

In figure 7 and table 5 the counts on the peripheral blood of dog 49 are presented. After the thoracic operation on May 1, 1935, there was a marked decrease in the lymphocytes and eosinophils, indicating temporary obstruction. A return to normal in the blood picture three weeks later indicated the establishment of collateral circulation. The results in this animal are typical of those obtained in the majority of the experiments. These results are entirely comparable to the findings of Lee.⁵

Owing to the fact that chylothorax develops in a higher percentage of cats than of dogs after occlusion of the superior vena cava, it was believed that these animals would be more suitable than dogs for the present study. That is, it seemed likely that there would be fewer collateral lymph vessels in cats than in dogs. Such, however, did not prove to be the case. Although the difference is not great, we have the impression that it is easier to produce lymphatic blockage in dogs than it is in cats.

In a previous report it was stated that chylothorax was not observed in the four experiments in which occlusion of the thoracic duct preceded ligation of the superior vena cava. Chyle was not found in the pleural

cavities in the experiments on six cats in this series in which attempts at blockage of the lymphatics was followed by occlusion of the superior vena cava. In one experiment the fluid was slightly whitish, but was not definitely chyle. This is in contrast to the experiments on cats previously reported in which chylothorax developed in fourteen of twenty-three animals in which ligation of the superior vena cava was the only operative procedure. In other words, it appears that chylothorax is much more likely to develop if ligation of the superior vena cava is not preceded by occlusion of the thoracic duct.

The question arises as to whether or not the sclerosing solution might be responsible for the alterations in the cellular composition of the blood. This point was tested by introducing sodium morrhuate into cats by the intravenous, intramuscular and intraperitoneal routes. The quantity injected was comparable to that used in the experiments on lymphatic blockage. Six such studies were performed. There was no alteration in the cellular picture in four of these. A slight decrease in the eosinophils and lymphocytes occurred in one of the experiments, and a somewhat more marked decrease in the eosinophils took place in the remaining study.

COMMENT

Any effort to evaluate these experiments must depend on the angle from which one approaches them. From the question of the lymphatic system being necessary to life, these experiments certainly indicate that when all of the evidence pointed to complete blockage, the animal was unable to survive. This does not, of course, explain the cause of death; it may have been due to a lowered resistance and a subsequent infection, as there is, of course, some evidence that the lymphatic system and the cells of the blood are concerned in the defense mechanisms of the body. The normal temperature and slow pulse of dog 15 certainly do not suggest infection. It is possible that in some animals, particularly animals like dog 28, death was due to injury of the tissue, which was secondary to blockage. Other explanations might be thought of to explain the direct cause of death; but it is obviously unsound to assume a necessity for such explanations, since at the moment we are dealing solely with a specific analysis of the necessity of the lymphatic system to life, and these experiments certainly speak in favor of such a thesis.

Analyzed from the point of view of the blood, these experiments indicate a close relationship between the lymphocytes and the eosinophils in terms of the effect of the operative procedures on their level in the circulating blood. It is obvious that the decrease in lymphocytes after obstruction of the lymphatics results directly by interference with the supply coming from the lymph nodes. The explanation for the sharp decrease in eosinophils is not at hand. It is true that the level of these

cells in the animals used in these experiments was abnormally high in terms of the usual concept. Whether a larger series of dogs and cats would demonstrate that we were dealing here with a group of animals having an unusually large proportion of eosinophils or whether these species always contain so many cells of this type is not certain. However, regardless of whether we were dealing with animals sensitized by foreign proteins or parasites or whether they were entirely normal, it is certain that obstruction of the lymphatics did markedly interfere with the maintenance of a normal level of eosinophils in the circulating blood.

It will be necessary to perform additional experiments before conclusions can be drawn in regard to the possibility of preventing the entrance of fat into the blood stream by lymphatic blockage. In the only experiment (dog 121) in which the studies of the fat in the blood have been completed, there was no evidence of the absorption of fat after the feeding of cream. In this connection, the loss in weight in two of the three animals in which satisfactory blockage was produced may be of interest.

After occlusion in cats of the thoracic duct in the chest, Lee⁹ observed collateral lymph channels which connected with the intercostal veins, and in one experiment a communication with a lumbar vein was observed. Many lymphaticovenous connections in the abdominal region have been demonstrated in the present study, and by far the most common site is with the inferior vena cava in the neighborhood of the entrance of the renal veins. In this connection, the following experience is of interest. Several operations had been performed on a dog in an effort to produce lymphatic blockage. The studies indicated that collateral channels had opened up sufficiently to convey the lymph to the blood stream. In view of the fact that these connections were usually with the inferior vena cava after the operations in the neck, chest and flank, it was decided that the inferior vena cava should be ligated above the renal veins. This was done, and chylothorax ensued. More than 5 liters of chyle was aspirated from the chest during the seven weeks that the animal lived. Autopsy revealed a pericardium distended with chyle and large white solid masses of coagulated material.

It is interesting that preliminary ligation of the thoracic duct lessens the chances of the development of chylothorax after occlusion of the superior vena cava. The most likely explanation seems to be that the occlusion of the thoracic duct causes the opening up of collateral channels to veins other than the tributaries of the superior vena cava.

SUMMARY

Experiments have been performed on fifty-two dogs and twenty-two cats in an effort to produce complete blockage of the lymphatics. A total

of two hundred and sixty-seven operations were performed. A variety of operative procedures were carried out, but in general these have consisted of blocking the lymphatic ducts in the neck and chest, of destroying the cisterna and of interfering with the drainage of the mesenteric lymphatics. The cellular picture of the blood was determined frequently in most of the experiments both before and at varying intervals after the operation. In many of the animals there was undoubtedly temporary obstruction, which was relieved by the opening of collateral lymph vessels; in these animals there was a marked temporary change in the blood picture, with return to normal. The essential alteration in the blood consisted of a marked decrease in the eosinophils and lymphocytes. In most of the animals in which evidence of blockage disappeared, lymphatic communications with the inferior vena cava were demonstrated at autopsy.

The findings indicate that complete lymphatic blockage was produced in three dogs (28, 15 and 121). These experiments have been described in detail. There was an almost complete disappearance of the lymphocytes and eosinophils from the blood stream. The animals lost weight rapidly and were killed when it was obvious that they were going to die. The picture at autopsy was striking. The lymphatics of the abdominal organs were markedly distended, and there was an extravasation of chyle into many of the tissues. No lymphaticovenous communications were demonstrated.

ARTHROPLASTY IN THE LOWER EXTREMITY

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Arthroplasty is an operation designed to reestablish a useful range of motion in an ankylosed joint or to increase the mobility in a joint with restricted function. In one form or another it has been used for probably a hundred years, but the results until recently were only occasionally successful, and the operation was performed only by the most adventuresome. In this country the greatest stimulus for its modern application was provided by the careful work, encouraging results and enthusiasm of the late Dr. John B. Murphy. In the last two decades many of the problems of arthroplasty have been solved by the technical improvements evolved by orthopedic surgeons, notably, Allison, Baer, Putti, Campbell, Henderson and MacAusland. There is much work yet to be done in perfecting the operative procedures and in improving the results. But at present one can decide with fair accuracy the type of case in which the operation should be performed, and one may expect a satisfactory issue in the majority of such operations.

THE PROBLEM OF ARTHROPLASTY

At the outset the fact should be appreciated that primarily the aim of arthroplasty is to create in a pathologic area a normally functioning joint. It would likely enough be impossible for a surgeon to design and establish a perfectly functioning joint were he to deal with absolutely normal tissues. But when he endeavors to make a joint among and from abnormal tissue, with many essential structures, such as the joint capsule, the ligaments, the bones and the articular cartilage wanting, defective, scarred or contracted, there should be little wonder that the end-result is often disappointing. The problem of arthroplasty, therefore, must be approached with an appreciation of one's limitations, and one must not expect the newly constructed joint to be anatomically, physiologically and mechanically perfect. While the goal must ever be to approximate and to imitate the normal, one should feel gratified when arthroplasty yields a stable and generally useful joint.

Read before the New York Academy of Medicine, Section of Orthopedic Surgery, April 17, 1936.

THE CHOICE OF PATIENT

As arthroplasty is distinctly an operation of election and not of urgent necessity, great care must be exercised in the selection of the proper type of patient. Parenthetically, it should be noted that there is need also for some attention to the choice of a surgeon. Arthroplasty is admittedly a difficult operation, requiring on the part of the surgeon special dexterity, speed, an accurate knowledge of the pathologic anatomy of ankylosis, an understanding of the physiology and mechanics of the function of the joint, patience in attention to technical details both during and after the operation and last but not least, a devotion to the gentle handling of tissues. One can successfully perform arthrodesis of either the hip or the knee with considerable indifference to the articular and periarticular structures, but not so in arthroplasty. Consequently, no surgeon should undertake to perform arthroplasty unless he is by temperament and training fitted to do so. Now as to the choice of patient. First, the patient must enthusiastically desire the operation, for only under such circumstances will he submit to the requisite careful preparation and doggedly persist and cooperate in carrying out the details of the prolonged convalescence. Second, the patient should be within the age period of from 20 to 45 years. It is useless, at least on the basis of the present knowledge, to perform arthroplasty on a child, for aside from the technical difficulties and the danger of disturbing the epiphyses, with resultant retardation of growth, it will be impossible to obtain the patient's cooperation in voluntarily exercising the new joint, and ankylosis will inevitably recur. Similarly, the aged person is an unfavorable subject because he rarely possesses the stamina to resist the enervating effects of arthroplasty or the pertinacity requisite for exercising the member which has been operated on. I have in the last few years successfully performed arthroplasty of the hip for advanced hypertrophic osteo-arthritis or ununited fractures of the neck of the femur in persons 50 and 55 years of age. But, by and large, a patient under 45 is preferable to one over 45. Third, a very stout person is an undesirable subject by reason of the evident technical difficulties involved in the accurate execution of the operation. Fourth, the patient must be in good general condition and free from any active focus of infection, be it ever so distant or mild, in the sinuses, urethra, pelvis or bones. For in the presence of any such lesion there is great likelihood of an infection in the area operated on, and to hazard arthroplasty is to court failure. Fifth, the social and financial status must warrant the venture of arthroplasty. Remembering that the joint resulting from arthroplasty on the lower limb is far from normal, one must not expect that it can be subjected to severe strain. Hence arthroplasty is rarely indicated in a laborer, though I am not unmindful that there have been cases recorded in which the person operated on has been able to resume

laborious work. Certainly no one would expect that ditch diggers or structural iron workers would be able to return to their customary labor after arthroplasty of either the hip or the knee. They often do not do so after far simpler operative experiences. One can expect that the patient will be able to engage in light work. Consequently, those in the leisure and white collar classes and those with sedentary occupations are the most favorable subjects. Then, too, since the convalescence from arthroplasty usually extends over many months, with an average duration of probably no less than a year, the patient undergoing such an operation must have the funds and the opportunity for staying away from his work to devote himself, with peace of mind, to the serious business of the gradual reestablishment of the function of the joint.

THE PRINCIPLES OF ARTHROPLASTY IN THE LOWER LIMB

In planning arthroplasty on the hip or knee one aims to obtain not only motion but stability of the joint in order to permit secure weight bearing. Enough bone should be removed to allow easy gliding of the articular ends. The articular surfaces should be smooth and fit fairly accurately. The capsule of the joint should not be stripped up any more than is indispensable to a satisfactory exposure of the bones in order that it may give adequate and reliable support to the newly formed joint. Arthroplasty should not be performed on a limb that is greatly deformed. For instance, if a hip is ankylosed in marked adduction and flexion, it is advisable to correct the deformity, place the limb in a neutral attitude and require the patient to walk about for several weeks or even months, depending on the severity and duration of the deformity, before undertaking arthroplasty. Similarly, a knee that is markedly flexed ought to be straightened by stretching or osteotomy before arthroplastic mobilization. It is important, too, to have a good circulation about the joint. Therefore, if there is extensive scarring, as after a burn, or loss of bone or muscle tissue, as after a severe fracture or osteomyelitis, this should be corrected or improved by plastic repair. The condition of the muscles adjacent to the joint is a vital factor. In the presence of severe atrophy of the muscle there is little opportunity for voluntary exercise of the proposed joint. Preoperative massage and voluntary contraction of the para-articular muscles are excellent for building up the muscle tone and strength necessary for satisfactory postoperative function.

GENERAL INDICATIONS AND CONTRAINDICATIONS FOR ARTHROPLASTY OF THE HIP OR KNEE

Before arthroplasty is undertaken, the general indications and contraindications should be considered.

1. There should be a special need for motion in the ankylosed joint. A single ankylosed hip or knee not only may cause little inconvenience but may be adequately strong and resistant for ordinary activities. A banker, dentist or clerk with one ankylosed painless knee or hip can conduct his business affairs, be active socially and even engage moderately in gymnastic exercises. On the other hand, a professional dancer must have, and a person of leisure may earnestly desire, the maximum of mobility. In such persons arthroplasty is warranted even for ankylosis of one joint.

2. The ankylosed joint must be free from an active or even a latent process of infection. Spontaneous pain, local heat, tenderness to pressure over the joint and sensitiveness on manipulation of the limb preclude arthroplasty. Considerable discussion has arisen in regard to the advisability of reestablishing motion in an ancient apparently healed tuberculous joint. Cases have been reported, especially by Baer and Albee, in which the results were successful. In my service at the Hospital for Joint Diseases I obtained a most satisfactory result from arthroplasty on a knee that had become ankylosed following what appeared clinically to have been a tuberculous invasion. Yet the surgeon so often sees severe exacerbations in healed (?) tuberculous joints after minor injuries that he should hesitate to introduce the trauma that inevitably accompanies arthroplasty. Baer,¹ in a paper on arthroplasty of the hip, stated "that twenty-one of these cases were operated on before 1918, and only six since. In the series before 1918, one-third of the cases resulted in relighting the tuberculosis, although this has invariably quieted down, with a subsequent stiff hip." One should at the very least wait until the joint has remained healed for several years and has been subjected to prolonged weight bearing without any signs of recrudescence of the disease and without any evidence in the roentgenograms of cloudiness, rarefaction or bone absorption.

3. The most favorable cases for arthroplasty are those in which complete ankylosis has followed trauma, such as a fracture, or suppurative infection, either gonorrheal or pyogenic.

4. The most unfavorable cases are those in which rheumatoid arthritis is present. This is so because of the patient's poor healing qualities, the great tendency to recrudescence of the arthritis and the presence of so much atrophy at the articular ends of the bones that there is likely to be inadequate repair of the bone.

5. Eburnation of bone, extensive loss of bone or scarring and fibrosis of the muscles controlling the joint are decidedly contraindications to arthroplasty.

1. Baer, William S.: Arthroplasty of the Hip, *J. Bone & Joint Surg.* 8:769-802 (Oct.) 1926.

SPECIFIC INDICATIONS FOR ARTHROPLASTY OF THE HIP

When the hip is affected by any of the following conditions, arthroplasty is specifically indicated.

1. Ankylosis of one hip in a good attitude. By a good attitude is meant one in which the limb is slightly flexed, abducted and rotated outward. However, should the hip be in moderate flexion, say 30 degrees, and adduction of 15 degrees, the operation is not necessarily contraindicated. When there is marked deformity, as a right-angled contraction, it ought to be corrected by stretching or osteotomy and arthroplasty, postponed for at least six months for two specific purposes: first, to make certain that the corrective manipulation has not lighted up a latent infection and, secondly, to allow the tissues, especially the bone, to accommodate their structures to function in the optimum position of the limb.

2. Ankylosis of both hips or involvement by a pathologic process which severely restricts motion. In this case one hip ought to be mobilized for improved function.

3. Ankylosis of both hips and both knees. If this deformity exists, one hip and the opposite knee should be subjected to arthroplastic procedures.

4. Hypertrophic osteo-arthritis of the hip occurring as an isolated idiopathic lesion and seen frequently in the third and fourth decades of life or as an end-result of a slipping of the epiphysis of the femur or of Legg-Perthes' disease. In such cases the active pathologic process has subsided, and there is no danger of reactivation. The head of the femur is greatly enlarged, but it can be pared down and shaped to resemble the normal bone. The cartilage in the floor of the acetabulum may be normal, or it may have been replaced by fibrous tissue which forms a favorable acetabular covering for the proposed arthroplasty. The margin of the acetabulum is sometimes encumbered with osteophytes, which can be excised fairly thoroughly. The capsule of the hip joint may be thickened but intact and can be preserved to assure stability. If the neck of the femur is shortened, it is advisable to combine with arthroplasty a Whitman reconstruction, the essential feature of which, for the purposes of this procedure, is a lowering of the great trochanter on the shaft of the femur to allow a satisfactory range of abduction. I have performed this type of operation, namely, a reconstruction arthroplasty, with great satisfaction.

5. Ununited fracture of the neck of the femur. In cases in which there is a sizable remnant of neck the effect of the Whitman reconstruction operation can be improved materially by surrounding the newly formed head and neck of the femur by a double layer of fascia lata. The result will improve both stability and the range of motion.

6. Ankylosing arthritis of the hip either as part of a generalized atrophic polyarthritis or as a complication of spondylitis deformans. Arthroplasty is specially indicated if both hips are affected.

SPECIFIC INDICATIONS FOR ARTHROPLASTY OF THE KNEE

Arthroplasty of the knee is specifically indicated when any of the following conditions are present:

1. Ankylosis of a single knee is complete extension or slight flexion resulting from an old pyogenic infection or a crushing fracture.

2. Ankylosis of both knees. In this condition at least one of the knees should be mobilized.

3. Ankylosis of both knees and both hips. When this condition exists, one knee and the opposite hip should be operated on to permit some function in the lower limbs besides standing.

4. Ankylosis of one knee as a result of a tuberculous infection. In this case arthroplasty should not be performed unless there is reasonable certainty that there is no residual disease of the bone, and the patient, after having had the hazards of the operation explained, chooses to assume the risk.

5. Rheumatoid arthritis. In this condition the ankylosis is incomplete, and the patient suffers from a painful limitation of motion. The prognosis of arthroplasty is only fair by reason of a usually coexisting polyarthritis, atrophy of the bones and the muscles, poor resistance with consequent liability to infection of the wound and the possibility of precipitation of an exacerbation of the old inflammatory process. Nevertheless, arthroplasty is warranted in selected cases in which motion in one knee is desired to permit increased physical activity and independence.

ARTHROPLASTY OF THE ANKLE

It is seldom that an arthroplasty of the ankle is contemplated or indicated. When only the tibio-astragalar joint is stiff there is enough elasticity contributed by the motions in the other joints of the foot to make walking fairly easy and comfortable. In those cases in which the tarsal joints as well as the ankle are ankylosed, as after a crushing injury or osteomyelitis, the tissues are so thoroughly distorted, the joint capsules and ligaments having been destroyed or ossified, that there is little opportunity for a successful operation.

TECHNIC OF ARTHROPLASTY

The principal feature of arthroplasty, after the proper molding and reshaping of the ends of the bones, is the interposition of a material to prevent contact and fusion of these ends. Many different substances

have been utilized, but it is, I believe, the consensus today that a double layer of autogenous fascia lata is the preferable medium to maintain separation of the extremities of the bones. In both the hip and the knee this double layer serves as a covering for the ends of the bones and provides a real joint space. The fascia should be carefully applied and securely fixed by a row of peripheral sutures which will assure its proper placement. That a new joint is actually formed is proved both by clinical experience and by the investigation of joints on which arthroplasty has been performed. Campbell opened up six such knee joints and found a true joint in every one. The interposed fascia became altered and acted as a synovial membrane. There was a definite joint space with synovial fluid. The articular bony surfaces were smooth and glistening and were covered with a fibrous tissue resembling the original fascia. The capsule was thickened. A section of fascia and bone examined microscopically revealed that beneath the fascia there was a layer of cartilage and fibrous tissue uniting it to the bone.

When fascia lata is not available, one can use a pedicled flap of muscle, fat and fascia, chromicized pig's bladder or prepared ox fascia. I have used both of the latter tissues but found that there was a greater hazard of postoperative infection and the liability of liquefaction and extrusion of the interposed tissue. It must, however, be remembered that the late Dr. William S. Baer used chromicized pig's bladder with remarkable success.

In no type of operation is it so imperative to observe the strictest asepsis as in arthroplasty, as infection spells failure. The technic must be as nearly atraumatic as possible. Every step of the operation must be planned in advance so that the tissues are not damaged unnecessarily. In particular, there should not be extensive stripping of the joint capsule, as that would weaken the joint and reduce the stability, which in the lower limb is of paramount importance. The control of hemorrhage is another important feature. In operating on the knee, an Esmarch bandage affords a bloodless field. In the hip all bleeders should be carefully clamped off or tied.

The method of approach to the joint is a matter of individual experience and preference. In the hip I like the half U or the anterior Smith-Petersen incision. Either gives a rapid and adequate exposure. In this joint I always form a ball and socket joint that approximates the normal joint. One must be sure to have a more or less capacious acetabulum, otherwise the friction of the bony surfaces will rapidly destroy the interposed fascia. If there is any remnant of the capsule of the hip, it should be retained and preserved. In the cases of osteoarthritis and ununited fractures, the capsule can be easily identified, incised and retracted without destroying its support after resuture at the termination of the operation.

In the knee several different incisions have been used. Baer used two vertical lateral incisions. Campbell approaches the joint through a curved anterior incision. Putti exposes the knee through an inverted Y incision. I prefer the median parapatellar incision, very properly called by Krida the general utility incision. In exposing the bones it is generally necessary to lengthen the quadriceps tendon. This can be done through a Z or inverted V cut into the tendinous portion of the rectus femoris muscle. The reformation of the knee can be attained through either of two current procedures. Putti, MacAusland and others, desiring to imitate the natural conformation of the knee, remodel the lower end of the femur into two condyles with an intercondyloid notch and the tibial extremity into two cup-shaped depressions with an intervening spinous projection to fit the condylar surfaces of the femur. Campbell and his followers perform an operation of convenience and practicality by modeling the lower end of the femur into a single condyle and shaping the tibia into an appropriate saucer-like depression. In my service at the Hospital for Joint Diseases the Campbell technic has been utilized with satisfactory results.

POSTOPERATIVE CARE

The postoperative care is a most important phase of arthroplasty. The primary requisite is immediate postoperative immobilization, which should be continued long enough to allow the tissues to recover from the operative trauma. This implies complete rest of the joint for a minimum of two weeks. The splinting is conveniently obtained by a plaster of paris spica bandage for the hip and a plaster of paris circular support or a brace for the knee.

In arthroplasty of the hip the limb should be fixed with the hip in flexion of 10 degrees and abduction of 25 degrees. It is well, also, to provide for traction under the plaster spica so that the newly formed articular surfaces may be kept separated. At the end of two or three weeks the spica is removed, and the limb is placed in a balanced swinging apparatus, either a Thomas brace or a plaster posterior shell. Passive and active exercises of the hip are initiated and carried out several times a day. Baking and massage of the hip and thigh reduce the postoperative edema and sensitiveness and favor function. The motion at the hip should be increased daily but should always be retained within a painless range. The limb should never be stretched or moved violently. After eight weeks the patient is fitted with a Thomas Caliper brace with a half-ring for support of the ischium. He now begins to walk with the aid of crutches and is encouraged to be about daily for increasing periods. The brace may be discarded in from four to six months, provided there is no pain on moving the hip or during weight bearing. The crutches may be replaced by a cane, which is used for a variable period. Physical therapy is advantageously continued for about a year.

In the case of the knee the original support, holding the knee in about 30 degrees of flexion, is left undisturbed for two weeks. The limb is then supported in a balanced jointed plaster splint or a Thomas brace with a Pearson attachment. Physical therapy is applied daily, and the patient is encouraged to move the knee. At the end of eight weeks the limb is fitted with a caliper brace and an ischial ring, and the patient is allowed out of bed for brief periods every day, being encouraged to walk with the aid of crutches. Gradually the crutches are replaced by a cane. At the end of about six months, if the knee is stable and painless, the brace may be left off and the amount of exercise slowly increased.

Arthroplasty is applied to joints that are either completely or partly ankylosed. In the latter group may be included hip and knee joints affected with rheumatoid arthritis and hips in which there is a hypertrophic osteo-arthritis. I have operated on eighteen hips disabled by hypertrophic osteo-arthritis. A detailed report of this experience will be published in a separate communication. The results have been encouraging. In fifteen of the eighteen cases there was either a good or a fair result, each patient having a stable hip, no pain or very little discomfort and a variable but satisfactory range of movement. In the remaining three cases, the result is unknown in two, and one patient died while at home about three weeks after the operation with symptoms suggestive of a pulmonary embolism. In some cases of hypertrophic osteo-arthritis the neck of the femur is very short. Consequently, in order to assure adequate abduction I have lowered the attachment of the trochanter on the shaft of the femur. I described this combination operation, that is, the reconstruction-arthroplasty, several years ago before this section. The satisfactory results of arthroplasty in cases of hypertrophic osteo-arthritis of the hip become particularly interesting because of the large number of such patients who seek relief from the condition.

CONCLUSIONS

1. Arthroplasty in the lower limb is useful in selected cases of ankylosis of the hip and knee.
2. Great care must be exercised in selecting both the proper type of patient and the proper type of joint to be operated on.
3. Arthroplasty requires meticulous attention to the operative technic and the postoperative therapy.
4. The best result is obtained by arthroplasty on a patient who has a single joint ankylosed from a crushing trauma or a pyogenic infection.
5. In cases of ankylosed healed tuberculous joints arthroplasty may be successful, but there is always the danger of lighting up a latent infection.

6. As reconstruction-arthroplasty, the operation may be employed in cases of ununited fractures of the hip.

7. Arthroplasty may be used with fair success on joints that are partly ankylosed from rheumatoid arthritis.

8. In cases of hypertrophic osteo-arthritis of the hip an arthroplasty or reconstruction-arthroplasty yields unusually good results.

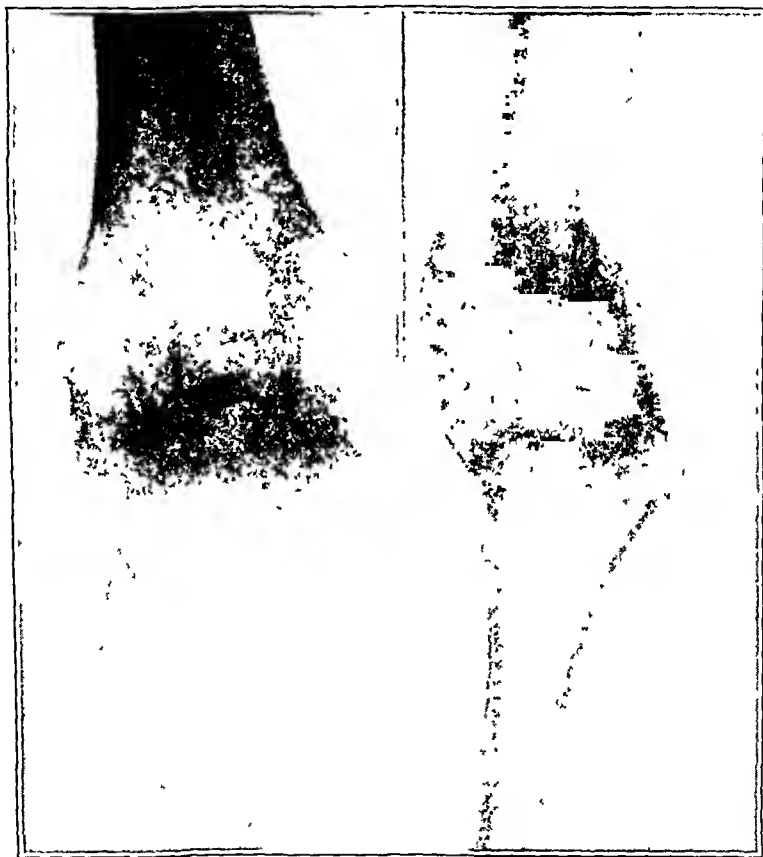


Fig. 1 (case 1).—Anteroposterior and lateral views of the right knee, taken on May 26, 1934, about one and one-half years after arthrodesis. Solid bony union and complete eradication of the joint are shown.

REPORT OF ILLUSTRATIVE CASES

CASE 1—Benno L. was admitted to my service at the Hospital for Joint Diseases on Oct. 22, 1932, at the age of 19. He had a painful swollen right knee. The history showed that he had injured the knee when $2\frac{1}{2}$ years of age. He recovered from this injury. But at the age of $10\frac{1}{2}$ he hurt the knee again, with consequent pain, swelling and stiffness of the joint, necessitating the use of a brace for over a year. Eighteen months before admission to the hospital he hurt the knee a third time, and since then the knee had been painful, swollen



Fig. 2 (case 1).—Anteroposterior and lateral views taken fifteen months after arthroplasty. There is a wide joint space. The articular surfaces appear very irregular in the anteroposterior but not in the lateral view.



Fig. 3 (case 1).—Photographs made on March 11, 1936, twenty-one months after arthroplasty. The patient is now of 22 years of age.

and flexed. During the past year he walked only with the aid of crutches. The roentgenograms showed marked erosion of the articular ends of the femur and tibia. The history of the repeated attacks of disability and the existence of erosion of the bone led to the diagnosis of tuberculosis of the knee.

On October 28 arthrodesis of the knee was performed. At operation softening and erosion of the bone were evident. There were no abscesses. The culture and microscopic examination of the removed tissue did not reveal any tubercles or tubercle bacilli. The result of the operation (fig. 1) was most



Fig. 4 (case 2).—Preoperative roentgenogram showing marked osteo-arthritis. The head of the femur is enlarged, flattened and irregular and probably represents an end-result of slipping on the epiphysis of the femur or of Legg-Perthes' disease.

satisfactory, as the patient obtained a solid fusion of the tibia and femur. Subsequently he became desirous of having his knee mobilized. This ambition was encouraged for the following reasons: First, an absolutely positive diagnosis of tuberculosis was not established. Second, since the knee had been fused he had been able to walk liberally and has had no discomfort in the knee and no sign of relighting of the inflammatory process. Third, the roentgenogram showed solid bony union and no areas of rarefaction, absorption or proliferation of bone

In June 1934 he was readmitted to the hospital, and arthroplasty was performed through a median parapatellar incision. The Campbell technic was used; that is, a single condyle was prepared at the lower extremity of the femur and the tibia was modeled into a single saucer-like depression. The patient had an uneventful convalescence. Roentgenograms (fig. 2) made in September 1935 showed an extensive joint. The articular surfaces appeared somewhat irregular, but the function was satisfactory. Photographs (fig. 3) made in March 1936, nearly two years after arthroplasty, showed the presence of 90 degrees of motion

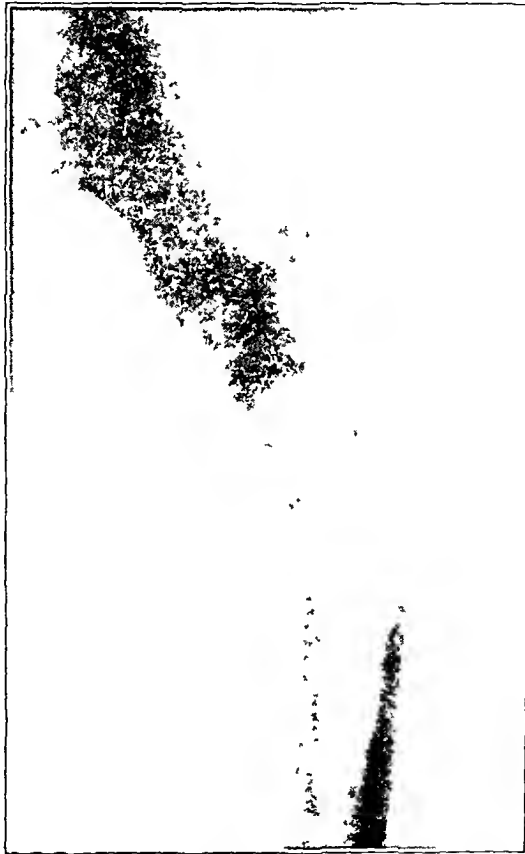


Fig. 5 (case 2).—Postoperative roentgenogram, showing reshaping of the head and neck of the femur. The articular surface of the head is fairly even and smooth. The irregular mass of bone above the neck of the femur is extra-articular.

in the knee. The patient walks without pain and without a limp and is able to stand on the operated leg—despite the fact that there is some lateral motion in the knee.

An interesting feature in this case is that, although the patella was not available at arthroplasty since it had been used at arthrodesis as a graft to favor fusion of the tibia and femur, this did not interfere with the ultimate function of the knee.



Fig. 6 (case 2).—Photographs made twenty-one months after arthroplasty. These show normal extension, flexion to 90 degrees and abduction to 30 degrees.

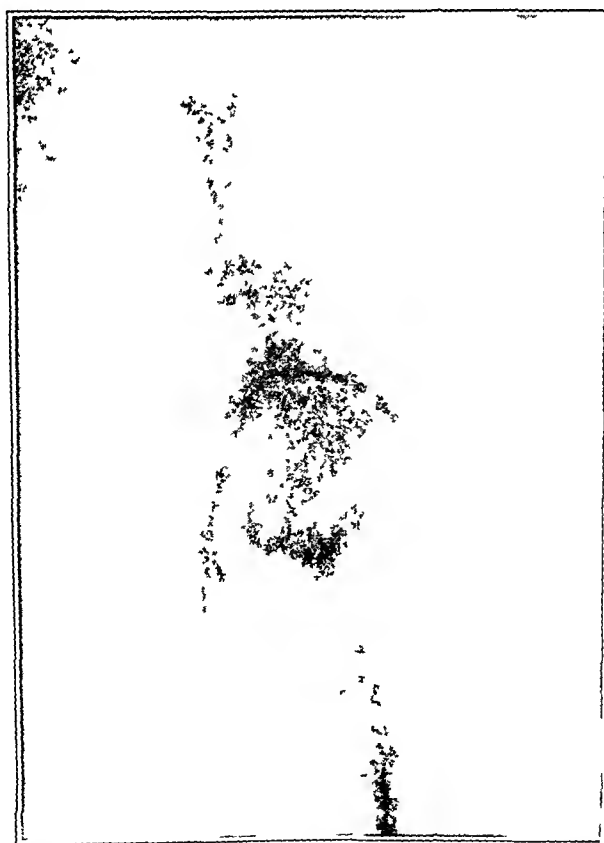


Fig 7 (case 3) —Preoperative roentgenogram of the left hip, showing marked osteo arthritis.



Fig 8 (case 3) —Postoperative roentgenogram taken seven months after arthroplasty The newly formed head of the femur, while small, is smooth and lies in a roomy acetabulum



Fig 9 (case 3) —Photographs showing the range of motion in the left hip after arthroplasty performed three years and three months previously.

CASE 2.—Gladys H., aged 33, was admitted to my service on June 4, 1934. Her chief complaint was pain in the left hip. This had started about six years previously and had continuously increased so that she was quite disabled at the time of her admission. Examination showed that the left lower limb was fixed in an attitude of 150 degrees of flexion and 10 degrees of adduction at the hip. There was no abduction and only a slight range of rotation. The roentgenogram (fig. 4) showed osteo-arthritis of the hip. The head of the femur was irregular and greatly enlarged, and the neck was shortened. The appearance suggested a late result of either slipping of the epiphysis of the femur or Legg-Perthes' disease during childhood.

Arthroplasty was performed on June 8 through an anterior Smith-Petersen incision. The patient had an uneventful convalescence and was discharged from the hospital on August 15, nine weeks after operation, walking with a caliper brace and crutches.

A roentgenogram (fig. 5) made on March 30, 1936, showed a good hip joint. The head of the femur, much reduced in size, lay completely within the acetabulum. There was an irregular mass of bone above the neck of the femur. This, according to other views, was extra-articular and seemingly did not interfere with motion.

The patient was reexamined on March 30. She stated that she had practically no pain in the hip and that she was pleased with the result of the operation because she can walk as much as she wishes, climb stairs, does all her own housework, including scrubbing of floors, and has, since the operation, been pregnant and delivered of a normal baby without difficulty. She walks without a limp. The original deformity is gone. She now has complete extension of the hip, flexion to 90 degrees, abduction to 30 degrees and a nearly normal range of rotation (fig. 6). There is $\frac{1}{2}$ inch (1.3 cm.) of shortening of the left lower limb.

CASE 3.—William M., aged 38, was admitted to my service on Jan. 15, 1933, complaining of a painful disability in the left lower limb. Examination showed that he walked with a marked limp. The left lower limb was flexed and adducted at the hip. He had a range of flexion from 155 to 110 degrees. He had no abduction and no rotation. A roentgenogram (fig. 7) of the left hip showed marked osteo-arthritis. The joint space was almost completely obliterated, the head of the femur was enlarged and there was some hypertrophy of the bone at the rim of the acetabulum.

Arthroplasty was performed on Jan. 20, 1933. Chromicized pig's bladder was used to envelop the newly formed head of the femur. The patient had an uneventful convalescence and was discharged from the hospital on March 21, two months after the operation. On October 17, seven months after the operation, a roentgenogram (fig. 8) showed a small but smooth head of the femur in a capacious acetabulum. The neck of the femur was very short. The function at the hip was satisfactory.

The patient was reexamined on March 30, 1936, three years and three months after arthroplasty. For the past two and one-half years he has been working as a deck hand on a ferry, doing laborious work. He works from eight to ten hours a day without feeling exhausted. He walks up and down stairs without any difficulty. He has a slight limp. He sits down and gets up from a chair with ease. He can extend the hip to 170 degrees; flex it to 125 degrees, abduct and adduct about 15 degrees and rotate the limb a few degrees inward and outward. The mobility of the hip is shown in figure 9.

PAINFUL COCCYX

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In 1859 Simpson dignified persistent pain in the coccyx with a new and since popular term, "coccygodynia." Unfortunately, coccygodynia is descriptive in an anatomic and a symptomatic sense only and discourages diagnosis on an etiologic basis. "The Standard Classified Nomenclature of Disease"¹ classifies painful coccyx as due to infection (tuberculosis or osteomyelitis) or to trauma (fracture, dislocation and contusion and tear of ligaments). This diagnostic classification also places the responsibility of finding an explanation for the pain on the physician and, fortunately, does not permit him to use the old non-diagnostic symptomatic designation.

HISTORY

The first recorded coccygectomy was done by Jean Louis Petit² in 1726, for what was probably tuberculosis. Blundell³ in 1840 advised resection of the coccyx for relief of pain of indeterminate origin. Nott⁴ (1844) receives the credit for the first resection in this country, in a patient with "neuralgia" due to caries of the coccyx. Simpson⁵ in 1859, as previously mentioned, described persistent pain in the coccyx as a separate entity under the term "coccygodynia." Von Scanzoni⁶ in 1867, inspired by Simpson's article, devoted two pages in his textbook to coccygodynia. These articles laid the foundation for what amounted to

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1. Logie, H. B.: Standard Classified Nomenclature of Disease, Compiled by the National Conference on Nomenclature of Disease, New York, Commonwealth Fund, 1935.

2. Petit, J. L.: A Treatise of the Diseases of the Bones, translated from the French, London, T. Woodward, 1726.

3. Blundell, J.: Principles and Practice of Obstetric Medicine, revised by A. Cooper Lee and Nathaniel Rogers, London, J. Butler, 1840.

4. Nott, J. C.: Facts Illustrative of the Practical Importance of a Knowledge of the Anatomy and Physiology of the Nervous System, New Orleans M. J. 1:57, 1844.

5. Simpson, J. Y.: Coccygodynia and Diseases and Deformities of the Coccyx, M. Times & Gaz. 1:861, 1859.

6. von Scanzoni, F. W.: Lehrbuch der Krankheiten der weiblichen Sexualorgane, Vienna, W. Braumüller, 1867.

a fad for coccygectomy, and for many years afterward it was a common operation. Nonoperative treatment, utilizing hot sitz baths, a soft cushion to sit on and massage, was revived following the fad for coccygectomy and used almost universally until after the turn of the last century. The nonoperative form of therapy again was not yielding satisfactory relief to many patients, and some surgeons once more advocated resection of the coccyx, while others stated that "operative removal of the coccyx was notably unsuccessful." Yeomans⁷ wrote "that many methods of treatment have yielded varying degrees of success is the best evidence of their unreliability." In 1914 he presented a new method of treatment, which consisted of the injection of 70 to 80 per cent alcohol into the sensory nerves of the coccyx to cause their degeneration, as had been suggested by Schloessner in 1907 and practiced by him with marked success for the relief of neuralgia of the trifacial nerve. For those patients who were not relieved of their coccygeal pain after the injection of alcohol, Yeomans advised operative resection. Gant⁸ in 1923 discarded the injection of alcohol and reported 90 per cent cures in 100 patients after coccygectomy. Suermondt⁹ in 1931 wrote that epidural injections of procaine hydrochloride had relieved some of his patients of their coccygeal pain. Yódice¹⁰ in 1932 and Kleckner¹¹ in 1933 injected 10 cc. of a 5 per cent solution of quinine and urea hydrochloride subcutaneously about the coccyx at intervals of one or two weeks, with relief from pain.

While a few other methods of relieving coccygeal pain have been reported, most surgeons have preferred nonoperative forms of treatment.

ANATOMY

The coccyx derives its name from the Greek word *κόκκυς* meaning cuckoo, based on the resemblance of the coccyx to a cuckoo's beak. Colloquially, it is called the tail or crupper bone. The four coccygeal vertebrae are united in the adult to form the coccyx. While four is the usual number of these rudimentary vertebrae, occasionally there are five and rarely three. As age advances the various pieces become united with each other, the three lower vertebrae uniting before middle life and the

7. Yeomans, F. C.: *Coccygodynia: Further Experiences with Injections of Alcohol in Its Treatment*, Surg., Gynec. & Obst. **29**:612, 1919.

8. Gant, S. G.: *Diseases of the Rectum, Anus and Colon, Including the Ileocolic Angle, Appendix, Colon, Sigmoid Flexure, Rectum, Anus, Buttocks and Sacrococcygeal Region*, Philadelphia, W. B. Saunders Company, 1923.

9. Suermondt, W. F.: *Die Behandlung der Coccygodynia*, Arch. f. klin. Chir. **167**:671, 1931.

10. Yódice, A.: *Treatment of Coccygodynia*, Arch. argent. de enferm. d. ap. digest. y de la nutrición **8**:733, 1932.

11. Kleckner, M. S.: *Coccygodynia: The Present Day Interpretation and Treatment*, Tr. Am. Proct. Soc. **34**:100, 1933.

upper somewhat later, as a general rule. In advanced life the coccyx may join with the sacrum, the union occurring earlier and more frequently in the male than in the female. In general, the coccyx is a triangular osseous formation, the whole bone being curved in a forward direction; it is concave in front and continues the curve of the sacrum. A detailed anatomic description of the coccyx, except for the relationship of the coccyx to the rest of the pelvis, is not considered necessary in this paper, as it is readily available to those who are not already familiar with this body. This relationship must be considered separately in the male and the female pelvis as there is a distinct difference.

The bones in the female pelvis are more delicate than those in the male pelvis. The sacrum is shorter and wider and is less curved; the greater sciatic notch has a greater diameter; the ischial tuberosities are wider apart and everted; the inferior aperture is larger, and the coccyx is more movable and hence slightly more variable in position.

The greater sciatic notch is wider in the female than in the male pelvis. In measurements made by Caldwell and Moloy,¹² on a group of 70 dried pelves (35 male and 35 female pelves), the average width of the greater sciatic notch taken at its greatest diameter was 40.8 mm. for the male pelves and 53.9 mm. for the female pelves.

The sacrum tends to follow the posterior limb of the ilium or of the superior angle of the greater sciatic notch, and the coccyx tends to follow the curve of the sacrum. Therefore, in the male pelvis, with the narrow greater sciatic notch, the inclination of the sacrum and coccyx is forward into the pelvic cavity or tucked in between the ischia. In the female pelvis the greater sciatic notch is wider; consequently the inclination of the sacrum and coccyx is generally backward (figs. 1 and 2).

ROENTGENOGRAPHIC STUDY

Roentgenograms of the pelves of 262 patients who had complained of pain in the coccygeal region were studied. Studies were also made of 100 males and 100 females who did not complain of a painful coccyx but who had had roentgenograms made because of symptoms referable to the lower part of the back. The lumbosacral area was studied to ascertain if there was any common variation usually associated with a painful coccyx. All of the roentgenograms were examined with particular reference to the coccyx (table 1).

12. Caldwell, W. E., and Moloy, H. C.: *Sexual Variations in the Pelvis*, Science 76:37, 1932; *Anatomical Variations in the Female Pelvis and Their Effect in Labor, with a Suggested Classification*, Am. J. Obst. & Gynec. 26:479, 1933.

The percentage of variations in the lumbosacral joint was about the same in the two groups of patients; consequently no common variation is associated with a painful coccyx.



Fig. 1.—Photographs showing the variation in the width of the sciatic notch in the male and the female pelvis; also the position the coccyx assumes in relationship to the rest of the pelvis.

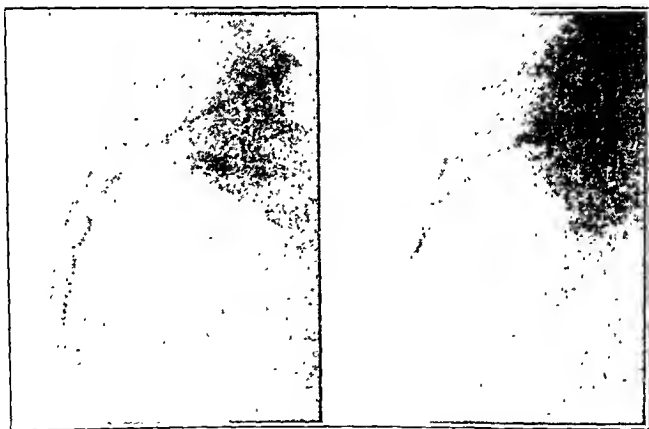


Fig. 2.—Lateral roentgenograms demonstrating the same anatomic relationship of the coccyx to the rest of the pelvis.

Malformations of the coccyx exist as the result of congenital influences and trauma, while variations are the result of congenital influences alone (table 2).

The number of coccygeal segments is variable, but four is the most common number. The number of segments found in the roentgen-

ographic study was approximately that found by Dieulaiffe¹³ in his osteologic study. He found 4 coccygeal vertebrae present in 79 per cent, 5 segments in 17 per cent and 3 segments in 4 per cent of 136 coccyges examined.

Roentgenographic findings are not significant in the explanation of painful coccyx except when a fracture, dislocation or osteo-arthritis is

TABLE 1.—*Variations in the Lumbosacral Joint*

Roentgenographic Picture	Absence of Painful Coccyx*	Painful Coccyx†
Unstable lumbosacral joint due to the following: Asymmetrical articulations, exaggerated lumbosacral angle, anteroposterior articulations.....	13S (69%)	15G (61%)
Unstable lumbosacral joint with posterior displacement, fifth lumbar on first sacral.....	3G (18%)	6G (22%)
Transitional lumbosacral joint (incomplete stabilization)	16 (8%)	26 (9.5%)
Spondylolisthesis	10 (5%)	8 (3%)
Lumbosacral area not shown on film.....	0	12 (4.5%)

* There were 200 patients (100 males and 100 females) in this group.

† There were 262 patients in this group.

TABLE 2.—*Anatomic Features of the Coccyx on Roentgenographic Study*

Roentgenographic Picture	Absence of Painful Coccyx*		Painful Coccyx†
	Males	Females	
No. of coccygeal vertebrae:			
3 segments present.....	11	12	39 (15%)
4 segments present.....	65	86	217 (83%)
5 segments present.....	4	2	6 (2%)
Fusion of intercoccygeal and sacrococcygeal joints.....	6	4	8 (3%)
Fusion of sacrococcygeal joint.....	15	10	37 (14%)
Fusion of intercoccygeal joints.....	5	3	12 (4%)
Fusion of the intercoccygeal joints except between the first and the second vertebrae.....	22	19	45 (17%)
Transitional sacrococcygeal joint:			
Unilaterally	7	8	29 (11%)
Bilaterally	1	1	18 (7%)
Lateral deviation of the coccyx.....	13	13	42 (16%)
To right.....	5	6	25 (10%)
To left.....	8	7	17 (6%)
Acute angulation anteriorly (over 45 degrees) of coccyx on sacrum.....	4	6	17 (6%)
Fracture of coccyx.....	0	0	12 (4%)
Dislocation of coccyx.....	0	0	6 (2%)

* There were 200 patients (100 males and 100 females) in this group.

† There were 262 patients in this group.

present. Almost any variation of the coccyx except a fracture or a dislocation that is noted in a patient with a painful coccyx can be matched in a roentgenogram of the coccyx of a patient who has never complained of pain in the coccygeal region.

13. Dieulaiffe, R.: Le coccyx; étude ostéologique, Arch. d'anat., d'histol. et d'embryol. 16:41, 1933.

Figures 3, 4, 5, 6 and 7 show various anatomic features of the coccyx as seen in roentgenograms.

To obtain good roentgenograms of the coccyx it is advisable to insist on the lower bowel being evacuated before making the plate, in order that fecal and gas shadows may not obscure the coccygeal field.

ETIOLOGY

Painful coccyx generally occurs after the age of 30 but may occur any time after puberty. In this series 7 per cent of the patients were under 20, 84 per cent between 20 and 50 and 9 per cent over 50 years of age. The youngest patient was 14 years of age, and the oldest, 68. Ninety-seven per cent of the patients were females. Trauma is a prominent feature, 89 per cent of the patients giving a history of a



Fig. 3.—Anteroposterior roentgenogram showing the first coccygeal vertebra fused to the sacrum and the distal three coccygeal vertebrae fused as one piece.

fall preceding the onset of pain. In the remainder the onset of pain was insidious and may have been due to repeated small traumas of which the patient was unaware. Often coccygeal pain is but one part of the picture in a patient having generalized arthritis. A few instances of tuberculosis and osteomyelitis of the coccyx have been reported in the literature, but none has been seen in this clinic. Darrah,¹⁴ Caubert¹⁵ and David¹⁶ have published reports of cases of tuberculosis of the coccyx, while cases of osteomyelitis of the coccyx have been men-

14. Darrah, R. E., cited by David.¹⁶

15. Caubert, H., cited by David.¹⁶

16. David, V. C.: Tuberculosis of the Os Coccygis, *J. A. M. A.* 82:21 (Jan. 5) 1924.

tioned by Blount¹⁷ and questionable cases, by Gaudier and Bertein¹⁸ and Grisel.¹⁹

During a period when over 5,000 persons with tuberculous or osteomyelitic infections of the bones and joints were seen at the New York Orthopaedic Dispensary and Hospital not one had involvement of the coccyx. This is evidence of its extreme rarity.

Except in patients with fracture, dislocation, osteo-arthritis, sacralization, osteomyelitis or tuberculosis of the coccyx, there has been an absence of pathologic evidence to explain painful coccyx. Explanation of the pain that occurs in those patients who do not fall in the afore-



Fig. 4.—Lateral roentgenogram showing the marked anterior angulation of the coccyx on the sacrum.

mentioned classifications can be only theoretical. These theories are based on the following etiologic factors:

1. Infection, such as a local manifestation of a generalized infection.
2. Symptomatic pain, i. e., a referred pain of central origin due to functional or organic disease of the central nervous system, such as hysteria, neurasthenia, asthenia, the traumatic neuroses, tabes dorsalis and toxemia (Yeomans).

17. Blount, W. P.: Osteomyelitis of the Coccyx, *J. A. M. A.* **91**:727 (Sept. 8) 1928.

18. Gaudier, H., and Bertein, P., cited by Blount.¹⁷

19. Grisel, P., cited by Blount.¹⁷

3. Injury, contusions or sprains of the coccyx.

4. Postnatal injury, such as occurred in 12 cases from pressure of the fetal head on the terminal nerves of the sacral plexus (Graefe, reported by Yeomans).



Fig. 5.—Roentgenogram showing marked lateral deviation of the coccyx, due probably to a hemivertebra.



Fig. 6—Transitional sacrococcygeal joint with sacralization on the left.

5. Neuralgic pain, i. e., that an initial trauma causes violent irritation of a nerve, which persists without any demonstrable lesion of the nerve (Marro, Pozzi and others, reported by Yeomans).

COMMENT ON ETIOLOGIC THEORIES

In regard to the first theory, the presence of arthritis is difficult to prove, but a painful coccyx in a patient with multiple arthritic joints is not uncommon and would lead one to suspect that the coccygeal pain is the result of the same factor or factors causing the generalized arthritis.

The second, or symptomatic, theory, in which the pain is considered due to any one of many functional or organic diseases of the central nervous system, has been the most widely accepted theory since painful



Fig. 7.—Anteroposterior roentgenogram showing a transitional sacrococcygeal vertebra with complete sacralization of the coccyx. The first coccygeal vertebra is fused to the sacrum, and the distal coccygeal vertebrae are fused as one piece.

coccyx has been thought of as a separate entity. Even in one of the most recent textbooks on neurology²⁰ there is a statement that "coccygeal neuralgia or coccygodynia is generally hysterical, and psychotherapy is the best form of treatment." The diagnosis of hysteria or neurasthenia is always dangerous and should never be made until all possible traumatic and organic lesions are ruled out. It frequently is

20. Wechsler, I. S : *A Textbook of Clinical Neurology*, Philadelphia, W. B. Saunders Company, 1935.

an admission of defeat on the part of the physician. It is true that the complaint is most frequently found in females and that neurasthenia and hysteria are perhaps more often associated with this sex; however, the female coccyx is more prominent posteriorly and is easily exposed to trauma. One does not make a diagnosis of hysteria in cases of pain in the knee, ankle or any other joint after injury because one has come to recognize that ligaments and muscles may be partially or even completely ruptured. Why should one not judge the painful coccyx following injury on the same basis? Sprain of the sacrococcygeal or intercoccygeal joints does not differ from a sprain about the ankle or knee, except that the symptoms may be of longer duration. Sprained ankles or knees can be placed at rest, whereas the coccyx is almost always in motion and subject to repeated small traumas. The coccyx is an integral part of the floor of the pelvis and affords attachments to many perineal muscles; therefore, with every act of defecation or urination, and during the act of sitting or rising from a sitting position, movement takes place in the coccygeal joints. This continual motion tends to prolong the traumatizing factors for a longer period than is the case in the usual sprained joint.

It is also unlikely that a lesion of the lumbosacral or sacro-iliac joint would cause referred pain to the region of the coccyx. Pain referable to a lesion of the lumbosacral or sacro-iliac region occurs as frequently in the male as in the female. During 1934, 640 patients were admitted to the hospital complaining of pain low in the back, and of these, 321 were females and 319 males. Therefore, if a painful coccyx is always due to referred pain from lesions in either of these joints, the pain should be referred as frequently in the male as in the female. Painful coccyx is most often present (97 per cent) in the female. There is no direct nerve leading to the coccygeal area from the lumbosacral nerve plexus except that which supplies the gluteus maximus muscle, which, in turn, has a small area of origin on the coccyx. There might be some excuse for considering lesions of the sacro-iliac joint as causing referred pain to the coccyx, as the fourth and fifth sacral nerves are contiguous to that joint. While osteo-arthritis is common in my opinion, mechanical strains of the sacro-iliac joint are uncommon, and osteo-arthritis is seldom productive of pain because of the limited motion in this joint.

Of 200 patients who were admitted to the hospital during 1929 to 1934 for pain low in the back and who subsequently underwent an operation to produce spinal fusion, only 9 (8 of them females) complained of a painful coccyx. The status of the coccygeal pain in these 9 patients, at least two years after the spinal fusion, is as follows: One has no pain or tenderness referable to her coccyx; 1 still has coccygeal pain but has pseudarthrosis of the fused spine; 3 still have coccygeal

pain but also have general arthritic pains; 2 still have coccygeal pain (roentgenograms of their coccyx being normal and the spinal fusion solid), and 2 have been relieved by coccygectomy when their coccygeal pain persisted after spinal fusion.

Disregarding the patient who still has pseudarthrosis of the fused spine, there are 7 of the 8 remaining patients with a painful coccyx after the spinal fusion. This is further evidence that lesions of the lower part of the back are not a common cause of referred pain to the coccyx. Spinal fusion has not in our experience permanently cured or even alleviated painful coccyx, except possibly by the rest in bed in a recumbent position, which relieved the coccyx of direct pressure.

The remaining three theories are all based on traumatism, either trauma from within the pelvis or direct external violence, such as a fall in the sitting position. In the majority of the cases of painful coccyx the pain can be explained on the basis of one of these theories.

Pressure of the fetal head on the coccyx and its overlying soft parts has been reported to have caused a localized neuritis. This is certainly not a frequent occurrence, as one finds no reference to it in textbooks on obstetrics. Furthermore, the patients who have presented themselves to this hospital with coccygeal pain immediately after delivery constituted less than 3 per cent of the total group of patients having a painful coccyx.

Contusions of the coccyx and its surrounding soft parts and sprains of the sacrococcygeal joint are probably frequent. These contusions and sprains are usually caused by direct trauma, such as a fall in the sitting position. A fall in this position is more likely to traumatize the coccyx in the female because of lack of protection afforded by the ischial tuberosities, which are wider apart than in the male, and the deep posterior position the coccyx occupies in the pelvis, whereas in the male, with the coccyx tucked in between the two ischii, the force of the fall would be felt first by the ischial tuberosities and then by the prominent sacrum.

The coccyx is surrounded by compact, fibrous and muscular structures; within this fibrous and muscular network on both sides lies the coccygeal plexus of nerves, and on the anterior aspect of the coccyx are the two sympathetic ganglions. Therefore, any injury to the soft structures about the coccyx may damage the adjacent nerves, and they may be involved in the later stages of scar formation, thereby being the cause of persistent neuralgia of the coccyx.

While fractures and dislocations of the coccyx are not frequent, they do not differ in their symptomatology from any other fracture, subluxation or dislocation. The range of motion in the sacrococcygeal joint is so great, except in persons over 50 years of age, in whom this

joint is usually fused, that an extreme injury would be necessary to produce such a lesion. The direction of the force is usually upward or in line with the forward curve of the coccyx, and this affords added mechanical protection to the coccyx. A fracture or posterior dislocation of the coccyx caused by pressure of the fetal head has not, to my knowledge, been reported in the literature, although excision of a resistant coccyx to permit passage of the fetal head has been reported.²¹ Several cadavers were placed in a prone position, and the coccyx was struck with a wooden mallet. This failed to produce a longitudinal fracture or dislocation and rarely caused a transverse fracture.²² Gross

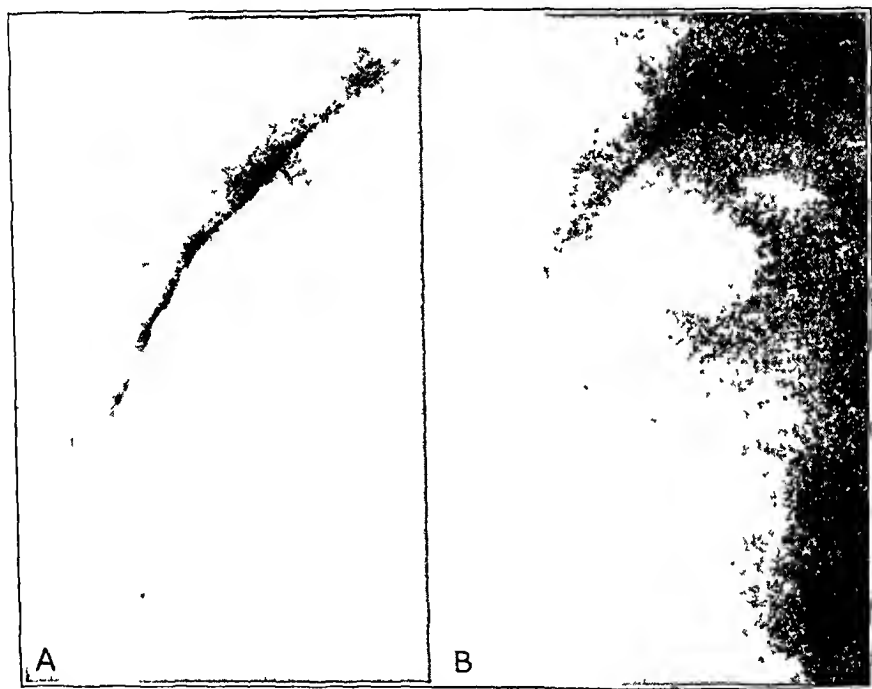


Fig. 8—*A*, appearance of the coccyx before any local injury. *B*, dislocation of the coccyx anteriorly after a fall in the sitting position, in the same patient, one year later.

and microscopic examination of coccyges removed in this hospital for supposed fractures have failed to reveal any evidence of them (figs. 8 and 9).

21. Graff, E.: Resection of Coccyx During Labor, *Wien. klin. Wchnschr.* **37**: 1260, 1924. Heckscher, S.: Ossification of Coccyx as Obstacle to Delivery, *Zentralbl. f. Gynäk.* **52**:2886, 1928. Niedermeyer, A.: Resection of the Coccyx During Labor, *Monatschr. f. Geburtsh. u. Gynäk.* **86**:190, 1930.

22. Becker, F.: Zur unfallmedizinischen Bewertung der Frakturen und Luxationen des Steissbeins und der traumatischen Coccygodynie auf Grund klinischer und experimenteller Untersuchungen, *Schweiz. Ztschr. f. Unfallmed.* **25**:338, 1931.

SYMPTOMS AND SIGNS

Pain is localized to the coccyx or the surrounding structures. The pain is increased by pressure, such as that elicited on sitting or on palpation. On palpation the pain is most commonly caused by pressure from behind on the coccyx and the lower end of the sacrum rather than by pressure on the tip or from in front. Pressure exerted in this manner corresponds to the direction of the original injury. Contraction of muscles, as in the act of sitting or rising from a sitting position, is painful. Muscles attached to the coccyx in contracting flex it and in so doing stretch the tissues affected by the original trauma. Pain is at times present during defecation or urination. There is nothing significant in the character of the pain, as this is quite variable. Patients frequently sit with one side of the pelvis elevated to remove pressure from the coccyx. With the index finger in the rectum and the coccyx grasped between it and the thumb, tenderness can be localized, and the general contour, mobility, angulation and deviation, if present, of the coccyx can be determined. Any local pathologic process, such as thrombosed hemorrhoids, anal fissures, fistula-in-ano and prostatitis, can be determined at this time.

DIFFERENTIAL DIAGNOSIS

A pilonidal cyst is the most common lesion from which a painful coccyx is to be distinguished. With a pilonidal cyst there is usually a dimpling of the skin or a discharging sinus. No pain is elicited on rectal examination if a pilonidal cyst is present, as this lesion is entirely dorsal to the sacrum.

A tumor of the cauda equina sometimes causes referred pain to the coccyx, but there may be present as well sensory changes and saddle anesthesia and paralysis, which may be flaccid or spastic. The pain is worse when the patient is lying down but not when sitting. There is an increase in the protein content of the spinal fluid.

PROGNOSIS

The prognosis of painful coccyx is good. If nonoperative treatment is used recovery usually takes place in from two to four weeks after treatment is instituted. In some patients the recovery is slower, the pain gradually subsiding over a period of from four to six months.

During the past ten years only 30 (11 per cent) of 278 patients with a painful coccyx were operated on in this hospital. They were patients in whom nonoperative measures had failed to give relief. Resection of the coccyx yielded satisfactory results.

TREATMENT AND END-RESULT

From 1924 to 1934 278 patients were admitted to the outpatient department of the New York Orthopaedic Dispensary and Hospital with the complaint of pain in the coccyx. The average age of these patients was 34 years. Two hundred and sixty-seven (97 per cent) were females. Two hundred and forty-seven (89 per cent) recalled having received an injury to the coccyx, usually by a fall in the sitting position. Curiously, the most common cause of the fall in this group of patients was slipping on an icy pavement. The interval between the time of injury and the time of the patient's admission to the hospital for treatment varied from three days to six months. Usually from two to four weeks had elapsed.



Fig. 9.—Roentgenogram showing a longitudinal fracture through the transverse process of the first coccygeal vertebra.

All of these patients were treated nonoperatively either before admission to this hospital or afterward. Nonoperative treatment consisted first of all in improving the patient's posture, having her sit erect, and pull the buttocks in under the trunk, thereby taking the superincumbent body weight off the coccyx and causing the soft parts surrounding the coccyx to act as a natural cushion. This particular procedure is much more satisfactory than having the patient carry a small pillow or rubber ring or strapping the buttocks tightly together. All of the last mentioned procedures have been employed. Hot sitz baths for from twenty to thirty minutes twice each day proved of value. Constipation, when present, was relieved by suitable laxatives. Local massage has proved beneficial to many of these patients. Steady but firm stretching of the coccyx posteriorly has been done on patients for

several consecutive visits, with relief from pain. This is done to overcome the spasticity of the muscles having their insertion on the coccyx and to prevent the formation of adhesions and contractures in the sacrococcygeal joint and the surrounding coccygeal structures.

Local injection of 70 to 80 per cent alcohol has been found unsatisfactory. Epidural injections of both physiologic solution of sodium chloride and a 2 per cent solution of procaine hydrochloride have been used. The use of the former solution failed in every instance to relieve the local pain, while the use of procaine hydrochloride gave only transient relief, that is, for a few hours or until the effect of the anesthetic had worn off. Injections of 5 per cent solution of quinine and urea hydrochloride have been recommended but have never been tried in in this hospital.

Of the 248 patients treated by nonoperative methods, 54 were examined by me from one to four years after the onset of their coccygeal pain. In this group of patients only 2 continued to complain of a painful or tender coccyx. One of the common physical findings in this follow-up examination was that fusion of the sacrococcygeal and intercoccygeal joints had taken place in a large number of the patients, and in the remainder there was limited motion. This limitation of motion in the coccygeal joints, coeval with cessation of pain, is additional evidence that the coccygeal pain was coming from a lesion of the joint. Injection of alcohol about the coccyx may not cause degeneration of the coccygeal nerves, but by causing scar tissue to form it may so limit motion of the coccyx that the pain is diminished or cured. In both of the patients who continued to complain of coccygeal pain, motion at the sacrococcygeal joint caused an identical pain.

Relief from pain was experienced within one month after the injury by 36 (67 per cent) of the 54 patients, by 11 (21 per cent) within two months and by 5 (9 per cent) within six months, and 2 (3 per cent) continued to have a painful coccyx.

These results would seem to indicate that the nonoperative form of treatment should be tried for a period of six months before operative resection of the coccyx is resorted to. However, this preoperative period may be shortened if an increase, or no abatement, in the coccygeal pain occurs as a result of nonoperative measures.

Thirty (11 per cent) of the patients in the total group had operative resection of the coccyx. Of the 30 patients, 27 were females and 3 males, their average age being 32 years. The youngest patient was 15 years of age, and the oldest, 53. The average duration of symptoms before resection of the coccyx was eighteen months. Patients were followed on an average for two years after coccygectomy. The shortest follow-up period was two months, and the longest, five years.

RESULTS OF COCCYGECTOMY

Twenty-two patients (74 per cent) were completely relieved of coccygeal pain.

Three patients (9 per cent) had only partial relief from pain.

In G. K. calcification developed at the site of the coccygectomy, and there were also symptoms of generalized arthritis (fig. 10).

G. S. obtained only partial relief from coccygeal pain. No post-operative roentgenograms were available.

L. S. was followed for only two months. She moved to another city, and it has not been possible to locate her.



Fig. 10.—*A*, lateral roentgenogram showing the coccyx before operative resection. *B*, lateral roentgenogram showing postoperative calcifications at the site of the coccygectomy.

Five patients (17 per cent) were unimproved.

In M. H. a local infection followed coccygectomy, and a sinus persisted for several months. Coccygeal pain continued, and nothing, including epidural injections of procaine hydrochloride (except temporarily), has relieved her pain. The pain is possibly caused by the coccygeal plexus of nerves being caught in scar tissue.

T. C. has continued to have coccygeal pain after coccygectomy. He also has a posterior displacement of the fifth lumbar on the first sacral vertebra, with an associated pain low in the back. Spinal fusion was advised, but the patient refused permission for the operation.

M. McK. underwent an operation for spinal fusion because of an acute lumbosacral angle and severely asymmetrical articulations. Coccygeal pain has persisted. The distal portion of the sacrum is prominent posteriorly, owing to the severe lumbosacral angulation.

M. B. has a calcified mass at the site of the coccygectomy, and coccygeal pain has persisted. The patient has refused to have this mass removed.

E. N. continued to have coccygeal pain for five months after operation, when she was last seen or heard from. There was no post-operative roentgenogram made of the site of the coccygectomy.

Nonoperative therapy, with the various methods adapted to the individual patient and applied vigorously and continuously, usually yielded satisfactory results. If coccygeal pain persists after from four to six months of this treatment, it is better to resect the coccyx.

COMMENT

Painful coccyx is so commonly the aftermath of an injury, such as a fall in the sitting position, that it is logical to consider the pain as due to local injury of the coccyx or its surrounding soft parts. Painful coccyx is most commonly seen in women, and an anatomic explanation has been presented to demonstrate that the coccyx is much more prominent posteriorly in the female pelvis and hence more liable to injury. The location of the pain is such that not only is it uncomfortable to the patient but she may neglect the condition for many weeks, as she may be loath to discuss such a lesion with her physician. There are a few other lesions that may localize the pain in the coccygeal area, but a careful physical examination can rule these out. The treatment should be nonoperative for a period up to six months. There is one exception to this, and that is a dislocation of the coccyx. When such a lesion is seen early the coccyx may be manipulated under anesthesia, and a reduction may be obtained. If nonoperative measures give but partial or no relief, the coccyx should be removed. Good results are obtained.

Painful coccyx is rarely of psychic origin, though neurasthenia may develop secondary to prolonged and severe pain.

300 Wainwright Building.

ARTIFICIAL MAINTENANCE OF CIRCULATION DURING EXPERIMENTAL OCCLUSION OF PULMONARY ARTERY

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Approximately one hundred and forty-two Trendelenburg operations for massive pulmonary embolism have been reported, and only nine of the patients operated on have left the hospital as cured.¹ This exceedingly high mortality is due to the critical condition of the patient and to the operative procedure, which entails the complete throttling of the great vessels leading from the heart for a brief period. Because of the difficulty in diagnosis and the uncertain prognosis, Nyström² advised postponing the operation until the patient is practically moribund. Then, as Churchill³ has stated, "the procedure could perhaps be more properly termed an immediate postmortem examination than a surgical operation."

Nyström and Blalock⁴ have demonstrated experimentally that occlusion of the pulmonary artery alone may be safely maintained for a longer period than occlusion of both the pulmonary artery and the aorta. Kiser¹ found that constriction of the afferent vessels of the heart in dogs allows a more prolonged interruption of the circulation to be safely carried out than occlusion of both the pulmonary artery and the aorta. This observation had previously been made by Låwen and Sievers⁵ in 1910. On the basis of their experimental results, Jeger⁶ in 1913 recommended compression of the venae cavae rather than the pulmonary artery and the aorta in the performance of the Trendelenburg operation. The

From the Surgical Research Laboratories of the Harvard Medical School at the Massachusetts General Hospital.

1. Kiser, W. J.: An Experimental Study of the Effects of Constriction of the Great Vessels of the Heart, *Surg., Gynec. & Obst.* **61**:765, 1935.

2. Nyström, G.: Experiences with the Trendelenburg Operation for Pulmonary Embolism, *Ann. Surg.* **92**:498, 1930.

3. Churchill, E. D.: The Mechanism of Death in Massive Pulmonary Embolism, with Comments on the Trendelenburg Operation, *Surg., Gynec. & Obst.* **59**: 513, 1934.

4. Nyström, G., and Blalock, A.: Contributions to Technic of Pulmonary Embolectomy: Experimental Study, *J. Thoracic Surg.* **5**:169, 1935.

5. Låwen, A., and Sievers, R.: Experimentelle Untersuchungen über die Wirkung von künstlicher Atmung, Herzmassage usw. auf die Lungenembolieoperation nach Trendelenburg, *Ztschr. f. Chir.* **105**:174, 1910.

6. Jeger, E.: *Die Chirurgie der Blutgefäße und des Herzens*, Berlin, August Hirschwald, 1913, p. 243.

clinical adoption of either of these principles, i. e., compression of the great veins or compression of the pulmonary artery alone, may diminish the hazard of the operative procedure, but the Trendelenburg operation will still remain a formidable undertaking.

A diminished cardiac output is the cause of death in massive pulmonary embolism.⁷ Because of the obstruction in the pulmonary artery the heart cannot adequately continue its function of transferring blood from the venous to the arterial side of the circulatory system. Blood accumulates in the veins, and a greatly diminished amount of blood enters the left side of the heart. The aorta is inadequately filled by the output of the left ventricle, and the blood pressure falls. Figure 1 is a graphic illustration of this condition. The pulmonary artery of a cat was compressed by a clamp until the venous pressure rose and the arterial pressure fell. This simulates the condition of the circulation in a patient at the time of a Trendelenburg operation. If at this point some of the work of the heart in transferring blood from the venous to the arterial side of the circulatory system were assumed by a mechanical pump, one might expect an improvement in the condition of the circulation. The congestion of the veins would be relieved, and the greater flow of blood into the arterial system might be expected to produce a rise in the arterial blood pressure. If any considerable amount of blood were thus transferred from the venous to the arterial system through an artificial circuit, it would be necessary to rid the blood of its excess carbon dioxide and supply it with oxygen.

The requirements are in general those of an apparatus for perfusion of isolated organs or limbs with whole blood, but there are certain essential differences. Perfusion of an isolated organ is carried out through a cannula tied in the main artery of the organ. The blood returning from the organ is easily collected from the main vein. Finally, a relatively large supply of blood is required for the perfusion apparatus itself.

On the other hand, a temporary mechanical aid to the circulation of a whole animal involves the insertion of cannulas into relatively small peripheral vessels, the sacrifice of which will not preclude the resumption of normal cardiorespiratory functions by the animal's own heart and lungs. Furthermore, the volume of blood necessary to fill the apparatus should be relatively small, preferably only a small fraction of the animal's total blood volume. With these points in view, an apparatus was devised to test on experimental animals the feasibility of the hypothesis outlined. The procedure employed was as follows. Venous

7. Gibbon, J. H., Jr.: Hopkinson, M., and Churchill, E. D.: Changes in Circulation Produced by Gradual Occlusion of the Pulmonary Artery, *J. Clin. Investigation* **11**:543, 1932.

blood was obtained from a cannula in the right jugular vein. This venous blood was exposed to oxygen and then returned to the animal's circulation through a centrally directed cannula tied in the right femoral artery.

APPARATUS

The apparatus designed to oxygenate the blood has already been described.⁶ The essential feature of the apparatus is a vertical revolving cylinder (fig. 2*A* and fig. 3). The stream of blood is directed at a tangent to the inner surface of the cylinder at its upper extremity. The revolution of the cylinder results in the distribution of a thin film of blood over its inner surface. The film moves downward by gravity, and the blood is collected in a stationary cup (*B*) at the bottom. The greater part of the space within the revolving cylinder is occupied by a hollow, closed, stationary cylinder (*C*), through the center of which passes a metal tube (*D*). A mixture of 95 per cent oxygen and 5 per cent carbon dioxide is conveyed through this tube to the bottom of the oxygenator. From here the gas

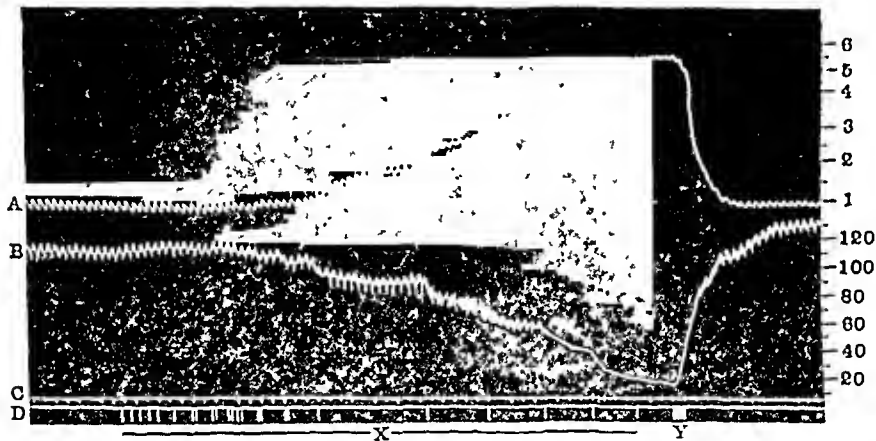


Fig. 1.—Kymographic tracing of the venous (*A*) and arterial (*B*) pressures during gradual complete occlusion (*X*) and release (*Y*) of the pulmonary artery. *C* is the time in five second intervals and *D*, the signal magnet. The figures to the right of the tracings represent the venous pressure in centimeters of water and the arterial pressure in millimeters of mercury.

passes up between the stationary and the revolving cylinders over the film of blood and escapes at the top. The apparatus was designed to meet the requirements of this particular problem. The ratio between the amount of oxygen introduced per minute into the blood and the volume of blood contained in the oxygenator is higher than in other oxygenators which have been described.⁸ It accommodates a flow of blood of 500 cc. or more per minute, and large variations in the rate of flow do not produce foaming.

Blood was moved through the artificial circuit by two pumps (*E*, *E'*). One (*E*) transferred the blood from the venous cannula to the oxygenator, while the other (*E'*) returned the blood from the oxygenator to the arterial cannula. The

8. Gibbon, J. H., Jr.: An Oxygenator for Blood with a Large Surface Volume Ratio, to be published.

pumps were based on de Burgh Daly's⁹ modification of the perfusion pump of Dale and Shuster.¹⁰ The principal feature of each pump was a rubber finger-cot (F, F'), which was alternately compressed and expanded by air. The finger-cot was placed in the blood circuit between two valves (G), which directed the flow of blood. Expansion and compression of the air in the finger-cot chamber was accomplished by an air piston pump (H). A small air compressor pump (2 inch bore [5 cm.] and $1\frac{3}{4}$ inch [4.4 cm.] stroke) was converted to this purpose by removing the valve in the cylinder head and sealing the valve in the piston head. The outlet at the top of the cylinder was connected by rubber pressure tubing with a small air chamber surrounding the finger-cot. The downstroke of the piston decreased the air pressure in the closed system, and the finger-cot (F) expanded, drawing blood into it through the inlet valve and closing the outlet valve. The upstroke of the piston compressed the air in the closed system and collapsed the finger-cot, which expelled its contained blood, closed the inlet valve and forced blood through the

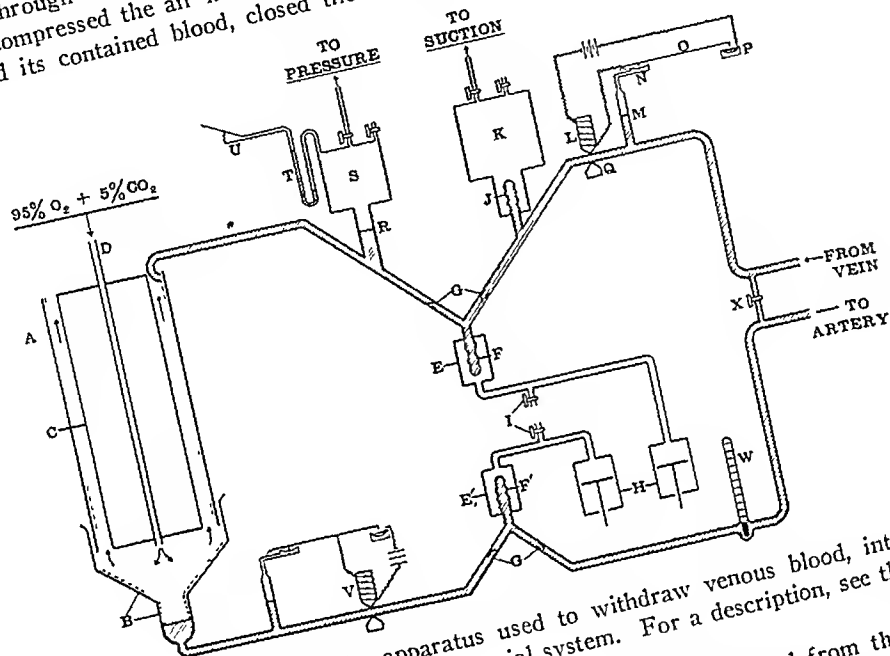


Fig. 2.—Diagram of the apparatus used to withdraw venous blood, introduce oxygen and return the blood to the arterial system. For a description, see the text.

outlet valve. A side arm closed by a needle valve (I) projected from the tubing between the air pump (H) and the blood pump (E). By adjusting this needle valve (I), varying degrees of leakage to and from the closed system could be produced. The amount of air leakage controlled the degree of compression and expansion of the finger-cot and hence governed the volume flow of blood through the pump. The venous blood pump (E) and the arterial blood pump (E') were similar in all respects. The air piston pumps were driven by a one-quarter horsepower electric motor. The motor was geared by means of pulleys to the piston pumps, so that the latter made 150 complete up and down strokes per minute. This approximates the rate of a cat's heart under barbitol anesthesia.

9. de Burgh Daly, I. A Seven Horse-Power Austin Engine Adapted as a Blood Pump, *J. Physiol.* **77**:xxxvi, 1933.
10. Dale, H. H., and Schuster, E. H. J.: Double Perfusion Pump, *J. Physiol.* **64**:356, 1928.

One of the early difficulties encountered was to obtain a rapid free flow of venous blood through the cannula in the jugular vein without sucking the thin wall of the vena cava into the tip of the cannula and so occluding it. When this occurred it produced an immediate cessation of flow and often resulted in the death of the animal. The difficulty was overcome by two means. The first consisted of converting the intermittent flow produced by the pump into a continuous one. By so doing, almost double the flow of blood could be obtained without increasing

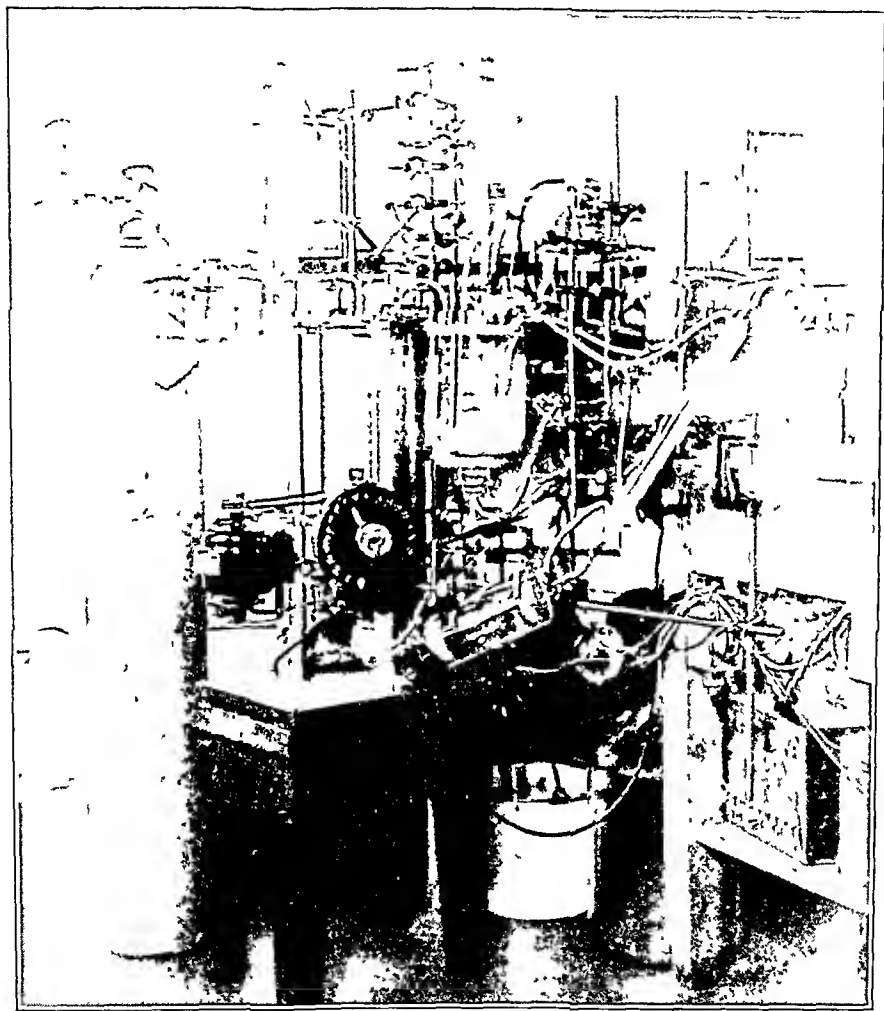


Fig. 3.—Photograph of the apparatus used. The vertical revolving cylinder of the oxygenator can be seen just to the left of the center.

the suction developed by the piston pump; conversely, the same volume output of the venous blood pump could be obtained with approximately one-half the velocity of the blood flow at the tip of the venous cannula. This decrease in the velocity of the flow through the venous cannula diminished the tendency of the wall of the vein to be sucked into the tip of the cannula. The conversion to a smooth flow was accomplished by connecting a rubber finger-cot (*J*) to the side arm of a Y tube inserted in the blood circuit between the inlet blood valve and the venous

cannula. The finger-cot projected into a closed air chamber (*K*) with a capacity of 1,000 cc. in which the air was maintained at a negative pressure just sufficient to expand the finger-cot (*J*) at the end of the expulsion period of the venous blood pump (*E*). With the intake phase of the venous blood pump (*E*), the finger-cot (*J*) partially collapsed, while with the output phase it reexpanded. There was thus maintained a continuous suction of blood through the venous cannula. The rubber finger-cot was used to separate the blood from the air in the chamber (*K*), because direct exposure of the blood to the low partial pressure of oxygen in the air chamber would have resulted in further removal of oxygen from the already venous blood.

The second method of dealing with occlusion of the tip of the cannula by the wall of the vena cava consisted in the use of an automatic magnetic clamp (*LQ*). The action of the clamp was controlled by the following device. A T tube with a vertical side arm (*M*) was placed in the blood circuit, between the magnetic clamp and the venous cannula. The top of the side arm was connected by narrow tubing with a small membrane manometer (*N*). The lever (*O*) of the manometer carried a wire which was bent at its end just above an insulated cup containing mercury (*P*). Contact of the tip of the manometer lever (*O*) with the mercury (*P*) completed a circuit through an electromagnet (*L*). This drew up the bar (*Q*), which compressed the tubing and thus prevented further suction by the venous blood pump. If the tubing between the vertical T tube (*M*) and the venous cannula was occluded by pressure with the fingers while the pump (*E*) was operating, or if the wall of the vein were drawn into the opening of the venous cannula, there occurred a sharp lowering of the meniscus in the vertical T tube and an increase in the negative pressure of the closed air system leading to the membrane manometer. The manometer lever was in consequence drawn down, closing the electrical circuit to the magnetic clamp and thus shutting off the suction of the blood pump from the venous cannula. With the suction cut off, the wall of the vein fell away from the tip of the cannula. Blood would again flow into the cannula and raise the meniscus in the T tube, thus raising the lever (*O*), breaking the electric circuit and allowing suction to begin again.

When the magnetic clamp began to act it was an indication that blood was being withdrawn too rapidly from the superior vena cava. Consequently, the air needle valve (*I*) controlling the flow of blood through the venous blood pump (*E*) was opened slightly to reduce the flow of blood. The magnetic clamp thus served two purposes. It prevented sudden, complete and relatively permanent occlusion of the cannula by the wall of the vein, and it also was an indication of how rapidly blood could be withdrawn from the superior vena cava.

Difficulty was encountered at first in constructing satisfactory valves (*G*) for the blood pumps. The flap valves described by Dale and Schuster¹⁰ could not be adapted to the small lumen of the tubing used. Satisfactory valves which could be used for months without deterioration or leakage were made by cutting four fifths of the way through the small end of a rubber cork at right angles to the long axis of the cork. The flap thus made was from 1 to 2 mm. thick. The edges of the flap were then slightly tapered. The flap was turned back, and a hole was bored through the center of the rubber cork to accommodate a glass tube, which extended to a point just beneath the flap. This provided a valve which had a quick action and did not leak.

A pulsatile flow of blood into the oxygenator produced foaming and splattering. Therefore, a second air chamber was introduced to convert the pulsatile flow into a smooth one. A Y tube with one branch (*R*) in a vertical position was placed in the blood circuit between the pump (*E*) and the oxygenator. The vertical

branch communicated with an air chamber (*S*) with a capacity of 500 cc. in which the air was maintained at a positive pressure. Blood was forced up into the vertical branch of this Y tube with every stroke of the pump. When the stroke was completed, the blood was forced down again by the pressure of the air in the chamber. By this means a practically smooth flow into the oxygenator was obtained.

The pressure in the air chamber (*S*) was recorded by a water manometer (*T*). The pressure readings gave some indication of the volume flow of blood through the venous blood pump because the resistance offered by the tubing between the tube (*R*) and the oxygenator was a constant factor. This was true only if the viscosity of the blood was constant and if the blood level in the tube (*R*) was maintained at a constant level with varying rates of flow by adjusting the pressure in the air chamber (*S*). In several experiments the excursions of this water manometer were recorded on the kymographic record by a small Brodie¹¹ bellows (*U*) connected to the manometer. The tracing was used merely as an indication of whether the flow through the artificial circuit was increasing or decreasing at any particular moment.

After the blood was exposed to oxygen on the inner surface of the revolving cylinder (*A*), it collected in the cup (*B*). From here it was withdrawn by the arterial blood pump (*E'*). Unless constant attention was paid to the output of the arterial blood pump, the blood level would either rise or fall in the cup (*B*) because of slight differences in the output of the two pumps (*E* and *E'*). Both occurrences were undesirable. If the blood rose in the cup, the volume of blood in the animal's own vessels was reduced. On the other hand, if the level fell to the bottom of the cup, bubbles of oxygen were drawn into the rubber tubing and pumped into the animal's arterial circulation with resultant gas embolism. Both these undesirable consequences were obviated by the use of a second automatic magnetic clamp (*V*), which operated on the same principle as the one previously described. A T tube was inserted between the cup (*B*) and the magnetic clamp (*V*). The top of the T tube was connected to the air chamber of a membrane manometer, the lever of which made and broke an electrical circuit operating the magnetic clamp. When the blood rose in the vertical side arm of the T tube, the circuit was broken and the magnetic clamp was opened. When the level fell, the arm of the manometer was depressed, the electrical circuit was closed and the magnetic clamp was shut. By this method the blood in the cup was prevented from falling below the desired level. The arterial blood pump (*E'*) was always operated at a larger volume rate of flow than the venous blood pump (*E*). This tended to make the level of blood in the cup fall. The fall was continuously checked by the magnetic clamp (*V*). The combination of driving the arterial blood pump at a larger volume flow than the venous pump, plus the constant checking of the magnetic clamp, maintained the level of the blood in the cup within a range of 1 cm.

The importance of maintaining the pulse pressure in the perfusion of organs has been pointed out by numerous investigators.¹² Hence a pulsatile flow through the arterial cannula was thought to be desirable. However, it was found that the pulse pressure produced by the pump was too large and also that the requisite amount of blood could not be forced through the arterial cannula with a com-

11. Brodie, T. G.: On Recording Variations in Volume by Air-Transmission: A New Form of Volume Recorder, *J. Physiol.* **27**:473, 1902.

12. Hooker, D. R.: A Study of the Isolated Kidney: The Influence of Pulse Pressure upon Renal Function, *Am. J. Physiol.* **27**:24, 1910. Gesell, R. A.: On the Relations of Pulse Pressure to Renal Secretion, *ibid.* **32**:70, 1913.

pletely intermittent flow. Consequently, a short section of wider, more elastic, rubber tubing was placed in the blood circuit between the outlet valve of the arterial blood pump and the arterial cannula. This resulted in a continuous flow with pulsatile increments, and the required amount of blood was easily injected through the arterial cannula.

Rough estimates of the flow of blood through the artificial circuit were made by timing the collection of 10 cc. of blood in the cup at the bottom of the oxygenator. Two horizontal marks were scratched on the lower glass portion of the cup (*B*), so that the volume contained between these marks was 10 cc. During the course of an experiment the level of blood was brought to the lower mark by cutting out the lower magnetic clamp and partially compressing the tubing with the fingers. The tubing was then completely occluded with the fingers until the level reached the upper mark, when the tubing was released and the automatic clamp started again. The time required for the level of blood to rise from the lower to the upper mark was measured with a stop-watch. Even when the lowest value obtained on three or four trials was used, the estimated flow was approximately 10 per cent under the actual flow (measured by collecting the fluid output of the arterial pump). Consequently, the estimates for the flow of blood made during the experiments are probably all slightly low.

The original pumps and tubing held 65 cc. apiece, and their output was only 300 cc. of water per minute. The output of blood was always less than the output of water because of its higher viscosity and greater frictional resistance. As the total blood volume of the cats on which the experiments were performed generally lay between 150 and 300 cc. (computing the volume as 70 cc. per kilogram of body weight), it was desirable to reduce the amount of fluid contained in the pumps and tubing. As finally perfected, the venous blood pump with all its tubing and connections, including the venous cannula, held only 21 cc. of fluid at any moment and was able to deliver 653 cc. of water per minute. The arterial blood pump with all its tubing and connections, including the arterial cannula, held only 20 cc. of fluid and was able to deliver 741 cc. per minute. At the larger rates of blood flow, the oxygenator held 35 cc. of blood on the sides of the revolving cylinder and flat surfaces of the cup. In addition, it was necessary to maintain a small reservoir of 15 cc. in the glass cup at the bottom of the oxygenator. Thus, the pumps, tubing and oxygenator contained a total volume of approximately 90 cc. of fluid while operating at a volume flow of from 300 to 500 cc. of blood per minute.

As the average cat weighing 3 Kg. has a volume of blood of only 210 cc., it was obviously impossible to withdraw enough blood (90 cc.) from the experimental animal to fill the pumps and oxygenator without producing a fatal depletion of blood in the animal's own vessels. Nor was it desirable to fill the pumps and oxygenator with salt solution, as this would rapidly leave the animal's blood vessels when injected into the femoral artery. Consequently, the apparatus was filled with 6 per cent solution of acacia in physiologic solution of sodium chloride. Then when blood was withdrawn from the superior vena cava the solution of acacia was simultaneously injected into the femoral artery, so that the volume of fluid in the animal's own vessels remained constant. The red cells in the average cat would be reduced theoretically by this procedure to roughly two thirds of their previous concentration. This anemia was avoided in a few experiments by the use of heparinized blood from another cat instead of the solution of acacia.

As much of the apparatus as possible was surrounded by a water bath through which water was constantly circulated at a rate of 1,500 cc. per minute by a

small rotary water pump. The water bath circulation has been omitted from figure 2 for the sake of simplicity. The venous blood pump and adjacent portions of the blood circuit were surrounded by water in an inverted bell jar (fig. 3). It was not possible to surround the moving parts of the oxygenator with water. The lower portion of the stationary cup at the bottom of the oxygenator was made of glass and sealed to the upper metal portion (fig. 3). The glass portion had a double wall. Water was circulated through the jacket between the inner and the outer wall. The arterial pump was also surrounded by water. In addition, a 40 cm. condenser jacket enveloped the tubing leading from the outlet valve of the arterial blood pump to the arterial cannula. The temperature of the water was controlled by two electric heating units, placed in a water reservoir with a capacity of 10 liters. The water in this reservoir was constantly circulated through the baths by the water pump. The temperature of the blood entering the femoral artery was recorded by a thermometer (fig. 2H) inserted in the tubing between the end of the condenser jacket and the arterial cannula. With the water bath maintained at approximately 42 C., the temperature of the blood as it entered the arterial cannula could be maintained constantly between 37 and 38 C. The rectal temperature of the animal was usually between 0.2 and 0.3 C. below the temperature of the blood entering the arterial cannula. The temperature of the water bath had to be maintained about 4 C. above the temperature of the blood because of the short exposure of the blood to the heating surfaces after it left the oxygenator in which most of the cooling occurred.

In order to maintain the acacia solution in the pumps and tubing at an even temperature, it was kept in circulation by the pumps during the operative preparation of the animal. This continuous circulation through the oxygenator and pumps was accomplished by opening the short circuit (fig. 2X) and closing the tubing leading to the arterial and venous cannulas. The oxygenator was warmed by the circulating acacia solution to a temperature above that of the room. Thus the cooling and heating factors were stabilized before blood entered the artificial circuit. To start the artificial circulation of the animal it was only necessary to open the tubing leading to each cannula and to close the short circuit.

METHOD

The experiments were performed on cats anesthetized by the intraperitoneal injection of a 10 per cent solution of sodium barbital, 0.45 Gm. per kilogram of body weight. In a few of the later experiments intratracheal ether was used. The blood pressure in the left carotid artery was recorded on a kymograph in the usual manner with a mercury manometer. The obstruction to flow of blood produced by a massive pulmonary embolus was simulated by compressing the pulmonary artery with a clamp. It was essential to have the animal breathing naturally in order to observe the effect of the experimental procedures on the respiration. Therefore, the pulmonary artery was exposed in the earlier experiments by using the heart preparation described by Drinker.¹³ A portion of the sternum was removed, and the pericardium was incised from the base to the apex of the heart. The cut edges of the pericardium were sutured to the opening in the wall of the chest. The operative procedure entailed opening both pleural cavities and hence required the use of artificial respiration. When the preparation was completed, artificial respiration was discontinued, and the heart and pulmonary artery were exposed in a naturally breathing animal. In the majority

13. Drinker, C. K.: A Useful Heart Method, J. Exper. Med. **33**:675, 1921.

of experiments a modification of Dinker's technic was used, which did not entail such a large incision or the cross cutting of as much tissue. Through an incision over the left fourth rib, the pectoralis major muscle was split in the direction of its fibers, the pectoralis minor muscle was divided and the left fourth costal cartilage and adjacent rib were removed subperiosteally. The left pleural cavity was opened through the bed of the cartilage and rib. A small transverse opening was made in the pericardium over the pulmonary artery, and the cut edges of the pericardium were sutured to the wall of the chest. This procedure involved less trauma and gave a better exposure of the pulmonary artery than that described by Dinker. A clamp (fig. 9) capable of very fine adjustments was used to compress the pulmonary artery.¹⁴ It was placed and held fixed in position about the pulmonary artery after the preparation of the chest was complete. The percentage of occlusion of the pulmonary artery produced by the clamp could be computed at any point during the compression of the artery.⁷

The right femoral artery was exposed through a small incision, and a cannula filled with saline solution was inserted in a central direction. The right jugular vein was exposed near the base of the neck, and a silver plated metal cannula with a blunt tip was passed into the vein in the direction of the heart for a distance of about 6 cm. The cannula was then firmly held by a clamp in the position in which it most naturally lay without tension. The clamp had two universal joints, which permitted changing the position and direction of the cannula during the experiment if so desired. Glass venous cannulas were used in some experiments, but they were not as satisfactory as the metal cannula because of their fragility. Autopsies were performed at the conclusion of every experiment, and the position of the tip of the venous cannula was noted. It was found to lie in the superior vena cava at varying positions between the junction of the innominate veins and the right auricle. In some experiments the respiratory movements were recorded by means of a fine silk thread connecting the skin of the anterior abdominal wall to a lever which wrote on the kymographic record.

During the preliminary operative procedures the temperature of the animal was maintained by a heating pad placed on the animal board. During the passage of blood through the artificial circuit the body temperature could be maintained by controlling the temperature of the water bath surrounding the artificial circuit. After the operative procedures were completed, heparin was injected intravenously in an amount sufficient to render the blood incoagulable. The preparation of heparin that was used contained 5 units¹⁵ per milligram, and the dose generally employed was 60 mg. per kilogram of body weight. A second, smaller, dose, 40 mg. per kilogram of body weight, was given an hour later. Thereafter it was usually unnecessary to inject more heparin, unless the observations were continued for two or three hours longer. In the majority of experiments a sample of blood was withdrawn at the time that the heparin was injected, and a hematocrit reading was made, Wintrobe's technic being used.¹⁶ At the conclusion of the experiment a second sample of blood was withdrawn, and another hematocrit reading was made. The supernatant plasma in the hematocrit tube was examined

14. Gibbon, J. H., Jr., and Churchill, E. D.: The Mechanical Influence of the Pericardium upon Cardiac Function, *J. Clin. Investigation* **10**:405, 1931.

15. Charles, A. F., and Scott, D. A.: Studies on Heparin: I. The Preparation of Heparin, *J. Biol. Chem.* **102**:425, 1933.

16. Wintrobe, M. J.: A Simple and Accurate Hematocrit, *J. Lab. & Clin. Med.* **15**:287, 1929.

for hemolysis. The degree of hemolysis was estimated by comparing the plasma with a Tallqvist hemoglobin scale. This gave a rough indication of the degree of hemolysis for comparison in different experiments.

OBSERVATIONS

Partial Occlusion of the Pulmonary Artery.—In the preliminary experiments the pulmonary artery was compressed until the blood pressure was lowered. The artificial circulation was then begun in an attempt to restore the blood pressure to its original level. Figure 4 is a portion of the kymographic record made during one of these experiments. Section 1 is a record of the blood pressure after the operative procedures had been completed and before the artificial circulation was started. At this time the pumps were circulating the solution of acacia through the oxygenator and across the short-circuiting tubing between the arterial and the venous cannulas. In the fifteen minute period between section 1 and section 2 the solution of acacia was mixed with the blood of the cat by closing the short circuit and opening the tubing to the arterial and venous cannulas. Blood was thus withdrawn from the vena cava, and the solution of acacia was injected into the femoral artery. The artificial circulation was continued for eleven minutes with the pumps running at a small volume output. The tubes leading to the cannulas were then clipped, and the short circuit was opened again. The solution of acacia was thus mixed with the animal's blood prior to the occlusion of the pulmonary artery. This was done so that the effects of the acute anemia thus produced could be observed apart from the effects of occluding the pulmonary artery and starting and stopping the artificial circulation. This experiment was performed before the volume of the fluid contained in the pumps had been reduced. At this time the pumps and oxygenator contained 180 cc., and although the cat was large (5.4 Kg.) the anemia produced by mixing this volume of acacia solution with the animal's blood must have been considerable. No hematocrit readings were made in this experiment, but an increase in the respiratory rate can be observed in the respiratory variations of the blood pressure at the beginning of section 2.

In the second section, during *A*, the pulmonary artery was gradually compressed until it was 71 per cent occluded. This produced a fall in blood pressure to a level incompatible with life, and respiration ceased. At *B* the artificial circulation was started, as can be seen in the upper tracing *F*. At *C*, a minute and a half later, respiration began again. At *D* the artificial circulation was stopped, as shown in the upper tracing *F*. The blood pressure subsequently fell, and respiration again ceased. At *E* the artificial circulation was started. The blood pressure then rose, and respiration was resumed at *G*. Thus in this experiment, with a partial

occlusion of the pulmonary artery, the artificial transportation of blood from the venous to the arterial system with the introduction of oxygen was essential to life.

Complete Occlusion of the Pulmonary Artery.—In twenty-one experiments the blood pressure was maintained at an adequate level, and the animal continued to breathe and the heart to beat while the pulmonary artery was completely closed for periods varying from fifteen minutes to two hours and fifty minutes. Figure 5 is a kymographic tracing made in one of these experiments. The first section illustrates the effect on the blood pressure of gradual occlusion (*A*) of the pulmonary artery before the solution of acacia in the pumps was mixed with the animal's blood. The occlusion of the artery was complete at *B*. Respiration had ceased, and the blood pressure had fallen to zero. At *C* the pulmonary

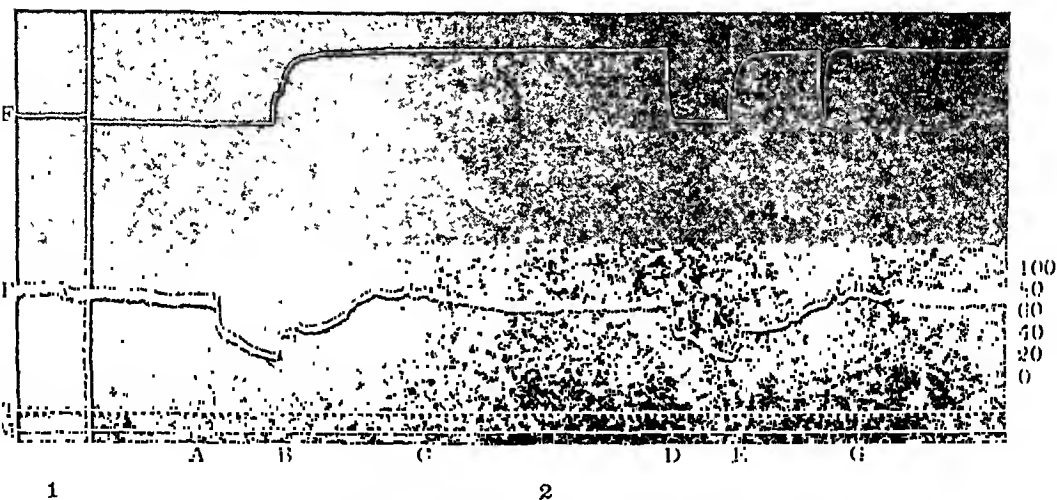


Fig. 4.—Kymographic tracing illustrating the effect on the blood pressure of partial occlusion of the pulmonary artery without and with the artificial circulation of blood. *F* is the pressure in the air chamber *S*, shown in figure 2. Elevation of the tracing indicates a greater flow of blood through the artificial circuit. *BP* is the pressure in the left carotid artery in millimeters of mercury; *T*, the time in five second intervals, and *SM*, the signal magnet tracing. For an explanation of *A* to *G*, inclusive, see the text.

artery was completely released, respiration was resumed and the blood pressure rose to its previous level. The solution of acacia in the artificial circulation was then mixed with the animal's blood by closing the short circuit and opening the tubing to the cannulas. The pulmonary artery was gradually compressed while a small amount of blood was flowing through the artificial circuit. As the compression of the pulmonary artery progressed, the volume of blood pumped through the artificial circuit was increased. The second section of figure 5 shows the terminal stages of compression (*D*) of the pulmonary artery. The

occlusion of the pulmonary artery was complete at *E*. It can be seen that the blood pressure was maintained at a level compatible with life and that the respiratory movements were regular but deeper than before, with an occasional deep sighing breath. Complete occlusion was continued for sixteen minutes in this experiment. During this time the blood pressure remained at the level shown, and the respirations continued to be regular but deep.

Figure 6 is an illustration of a high blood pressure maintained during complete occlusion of the pulmonary artery. Section 1 is a record of the blood pressure and respiration before the blood was mixed with the solution of acacia in the pumps. The second section shows the terminal stages of compression (*A*) of the pulmonary artery while blood was passing through the artificial circuit. The occlusion was

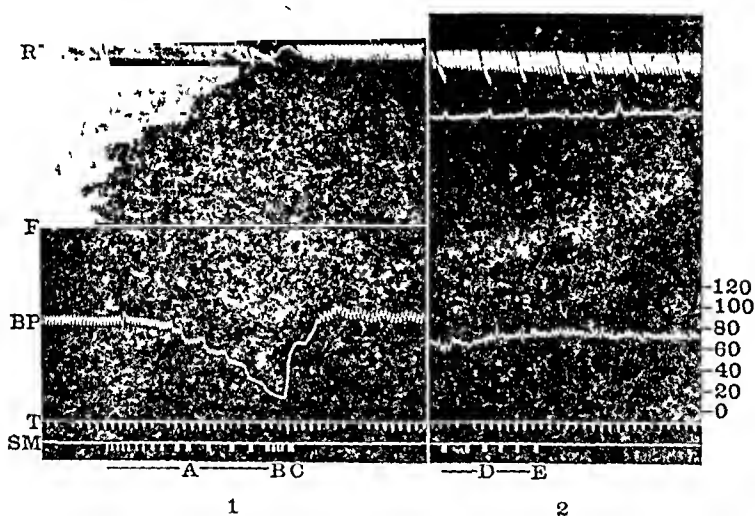


Fig. 5.—Kymographic tracing illustrating the effect on the blood pressure of complete occlusion of the pulmonary artery without and with the artificial circulation of blood. *R* is a tracing of the respirations. *F*, *BP*, *T* and *SM* are the same as in figure 4. For an explanation of *A* to *E*, inclusive, see the text.

complete at *B*. The third section was made during the tenth minute of complete occlusion of the pulmonary artery. The blood pressure was 110 mm. of mercury, and the respiratory movements were deep and slow. The pulmonary artery was released nine minutes later because of a break in the water bath circulation surrounding the artificial circuit.

Figure 7 is a record of a more prolonged occlusion. The first section shows the blood pressure and respiration before the blood and the solution of acacia were mixed. The second section shows the terminal stages of compression (*A*), which was complete at *B*. The third section is a record of the blood pressure and respiration during the fortieth minute of complete occlusion of the pulmonary artery. The respiratory

movements were slow and deep, and the blood pressure varied between 100 and 140 mm. of mercury. The large variations in blood pressure were due to a lack of sensitivity in the control of the magnetic clamp below the oxygenator (fig. 2 *V*). This was corrected in subsequent

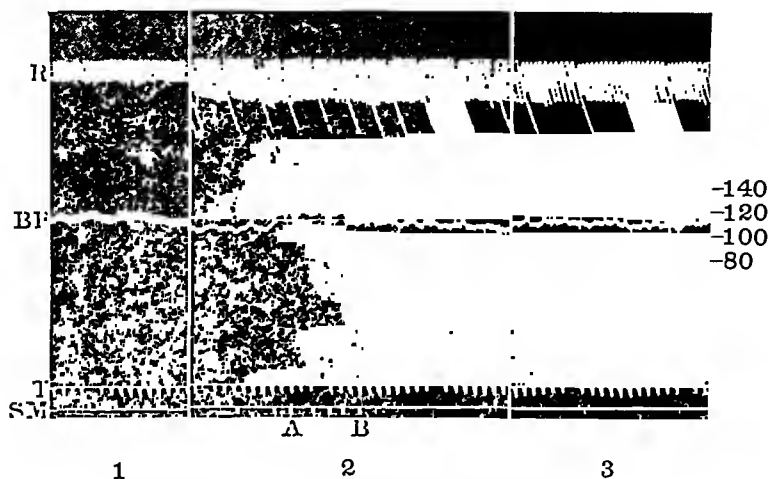


Fig. 6.—Kymographic tracing illustrating the maintenance of a high blood pressure by the artificial circulation of blood during complete occlusion of the pulmonary artery. *R* and *BP* are the same as in figure 5. For a further description, see the text.

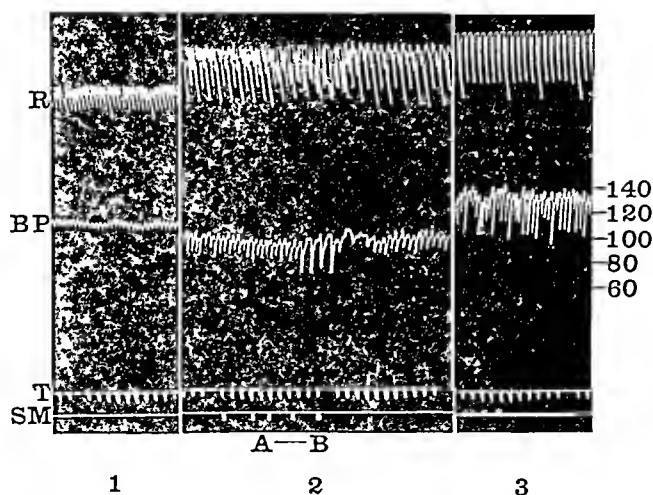


Fig. 7.—Kymographic tracing illustrating the maintenance of the blood pressure and respirations by the artificial circulation of blood during complete occlusion of the pulmonary artery for forty minutes. *R* and *BP* are the same as in figure 5. For a further description, see the text.

experiments, and the pressure swings due to the action of the magnetic clamp were generally less than the normal respiratory variations in blood pressure.

Figure 8 is a kymographic record of the experiment in which the pulmonary artery was completely occluded for the longest period. The first section shows the blood pressure before the blood and solution of acacia were mixed; the second section shows the maintenance of the blood pressure when the pulmonary artery was completely occluded at *A*. The respiratory movements were deep and approximately at the original rate. The third section is the record made during the sixty-eighth minute of complete occlusion of the pulmonary artery. Traube-Hering waves were beginning to appear in the blood pressure, the respiratory rate had become slow and the respiratory movements were not as deep as before. The fourth section was made during the one hundred and twenty-eighth minute of complete occlusion. Traube-Hering waves were marked, and the respiratory rate was still slower.

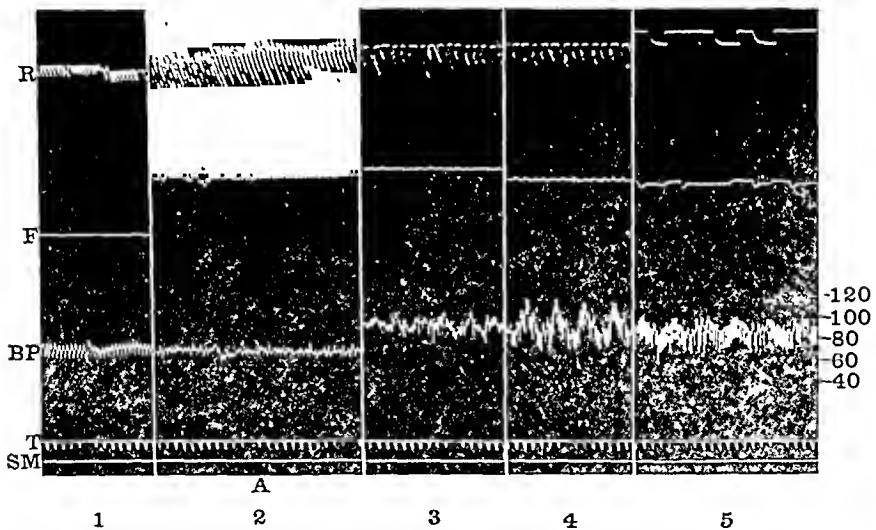


Fig. 8.—Kymographic tracing illustrating the maintenance of the blood pressure and respirations for two hours and thirty-eight minutes with the pulmonary artery completely occluded. *R*, *F* and *BP* are the same as in figure 5. For a further description, see the text.

The fifth section was made during the one hundred and fifty-eighth minute of complete occlusion. The respiratory movements were very slow and irregular. The last breath was taken two hours and fifty-one minutes after the pulmonary artery had been completely occluded.

In these experiments there can be no doubt that the pulmonary artery was completely closed by the clamp. Figure 9 is a drawing of the clamp used. It consists of a tube (*A*), to which the upper jaw of the clamp is fixed. The rod *BC* passes through the tube *A* and is bent to form the lower jaw of the clamp. The upper half of *BC* is wormed and articulates with the knurled nut *D*. An eighth of a turn of the nut moves the

lower jaw of the clamp 0.079 mm. The portion of the rod *BC* bent to form the lower jaw of the clamp is very rigid. The fine worming of the rod *BC* offers an enormous mechanical advantage to the operator moving the knurled nut, and the nut was always tightened firmly when the artery was completely occluded. The jaws of the clamp were of sufficient length to extend beyond the edge of the flattened compressed artery. Furthermore, both the artery and the jaws of the clamp were always under direct vision, so that by no possibility could an unoccluded portion of the artery project beyond the extremities of the jaws. Finally,

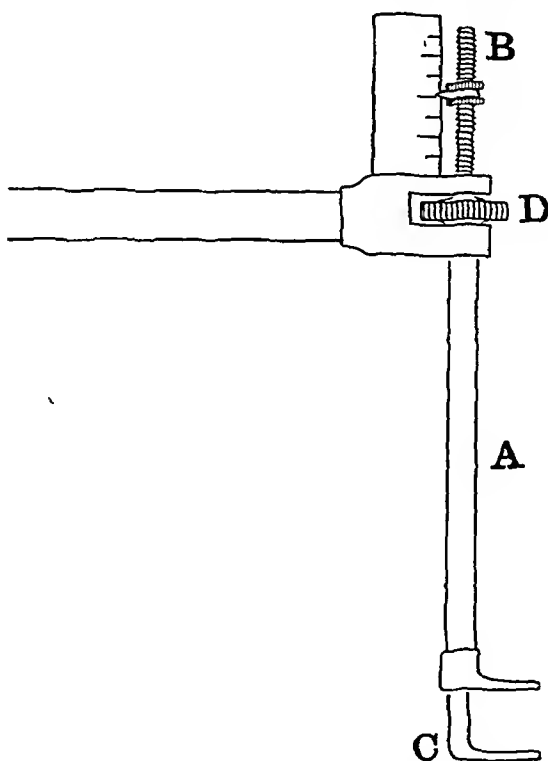


Fig. 9.—Drawing of the clamp used for compression of the pulmonary artery. For a description, see the text.

in the excised heart with the artery compressed by the clamp the pressure in the right ventricle could be raised to 240 mm. of mercury without any fluid being forced through the compressed pulmonary artery. At such a pressure the wall of the right ventricle was distended almost to the point of rupture, and this pressure was obviously many times higher than any that could be developed during life.

Recovery After Complete Occlusion of the Pulmonary Artery.—In a few experiments an attempt was made to study the capacity of the animal to recover spontaneously after a period of complete occlusion

of the pulmonary artery. In three experiments with complete occlusion of the pulmonary artery for thirty, thirty-three and thirty-nine minutes, respectively, the animals were observed for more than two hours after the release of the pulmonary artery and cessation of the artificial circulation. Figure 10 is the kymographic record made in one of these experiments. Section 1 shows the respirations and blood pressure before mixing the solution of acacia and the blood. The indication of flow (*F*) appears on the record because the solution of acacia was being circulated through the pumps and oxygenator. The second section shows the blood pressure during the thirtieth minute of complete occlusion of the pulmonary artery. At this time the flow of blood through the artificial

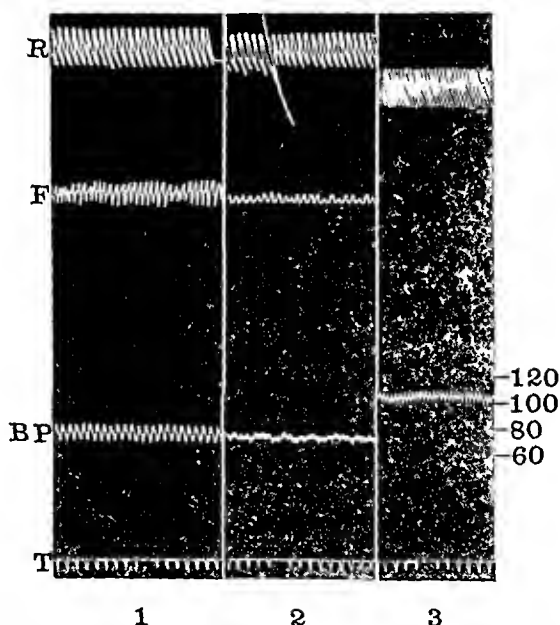


Fig. 10.—Kymographic tracing illustrating the natural maintenance of the blood pressure two and one-half hours after a thirty-nine minute period of complete occlusion of the pulmonary artery. *R*, *F* and *BP* are the same as in figure 5. For a further description, see the text.

circuit was estimated to be 300 cc. per minute. The pulmonary artery was released nine minutes later. The third section is a record of the blood pressure and respiration two and a half hours after the pulmonary artery had been released and the artificial circulation stopped. As can be seen, the blood pressure was maintained at an adequate level by the animal's own heart, and the respiration movements, although deep and rapid, were quite regular. In this experiment, after the artificial circulation had been stopped, the mixture of blood and solution of acacia remaining in the pumps and oxygenator was removed, and some of it

was centrifugated to concentrate the red cells. Eighteen cubic centimeters of the mixture of blood and the solution of acacia and 18 cc. of this concentrated suspension of red cells were returned to the animal's circulation. Even so, the hematocrit reading, taken immediately after this record when the experiment was terminated, showed only 27 per cent cells.

The protocol of the foregoing experiment (30 A) follows. The experiment was performed on May 10, 1935, on a cat weighing 2.86 Kg.

Time	Temp. of Water Bath, C.	Temp. of Fluid in Artificial Circuit, C.	Rectal Temp., C.	Notes
A. M.				
9:52				12.8 cc. of a 10 per cent solution of sodium barbital injected into peritoneal cavity
11:29				Tracheotomy performed; cannula tied into trachea; Drinker heart preparation started
11:52				Artificial respiration begun
P. M.				
12:23			36.8	Artificial respiration stopped; Drinker heart preparation completed
1:07			38.0	
1:17				Right jugular vein and right femoral artery exposed
1:40				While clamp was put around pulmonary artery, right side of heart became distended and blue and respirations ceased; clamp removed and artificial respiration started
1:43				Heart recovered normal tone; artificial respiration stopped; cat breathing normally
1:50	39.4	31.0	37.2	Circulation of solution of acacia by pumps through shunt started; oxygenator started; heating pad turned to "low"
1:58				Clamp in place about pulmonary artery
2:05				175 mg. of heparin (60 mg. per kilogram of body weight) in 8.5 cc. of saline solution injected intravenously; hematocrit sample no. 1 taken
2:10	41.3	36.5	37.0	
2:33				Cannula in jugular vein
2:40	42.8	38.7	37.2	Cannulas in femoral and carotid arteries
2:55	41.2	36.7	37.4	Heating pad turned off
3:02	40.2	36.8	37.6	

Time	Temp. of Water Bath, C.	Temp. of Fluid in Artificial Circuit, C.	Rectal Temp., C.	Notes
3:03				Flow of 95% oxygen 5% carbon dioxide started into oxygenator at rate of 5 liters per minute
3:04	40.0	36.7	37.5	
3:07				Shunt closed and tubing to arterial and venous cannulas opened, starting artificial circulation
3:09	40.8	37.2	37.4	
3:12				Compression of pulmonary artery begun; five turns of knurled nut on clamp (17% occlusion)
3:13				Three full turns and three half turns of nut (66% occlusion)
3:15	40.7	36.3	37.1	
3:16				Four quarter turns of nut (83% occlusion)
3:18				Rate of revolution of oxygenator increased
3:20	41.0	36.6	36.8	One quarter turn of nut (87% occlusion); color of arterial blood bright red now
3:22				Three quarter turns of nut; pulmonary artery completely occluded; arterial blood bright red
3:23				Rate of revolution of oxygenator reduced, because of tendency of blood to foam at faster rate
3:24	41.3	36.8	36.8	
3:28				160 mg. of heparin given intravenously
3:30	42.0	36.8	36.8	Right ventricle moderately distended; heart rate is synchronous with blood pump
3:32				Oxygenator rate, 467 revolutions per minute; moderately deep respirations
3:34				Blood flow through artificial circuit timed; 10 cc. in 2.3, 2.9, 2.2 and 2 seconds; blood flow about 300 cc. per minute
3:37	42.4	37.1	36.8	
3:41	42.6	37.3	36.8	
3:45	42.2	37.1	36.8	
3:49	42.2	37.2	36.8	
3:52	42.3	37.3	36.8	
3:55				5 cc. of acacia solution added to blood in artificial circuit
3:56	42.7	37.3	36.8	
4:00				Oxygenator rate increased to 519 revolutions per minute; no frothing; arterial blood a good red

Time	Temp. of Water Bath, C.	Temp. of Fluid in Artificial Circuit, C.	Rectal Temp., C.	Notes
4:01				Venous cannula broken; clamp compressing pulmonary artery widely opened; artificial circulation stopped
4:05				Broken cannula removed and jugular vein ligated
4:09			36.4	Heating pad turned to "high"
4:15			36.5	
4:21			37.2	A little bloody fluid from artificial circuit injected into femoral artery; heating pad turned to "low"
4:31			37.8	Heating pad turned off
4:43			37.8	
4:48			37.7	
4:59			37.2	9 cc. of bloody fluid from artificial circuit injected into the femoral vein; heating pad turned to "medium"
5:01			37.2	Heating pad turned to "low"
5:28				9 cc. of same fluid injected into the right femoral vein
5:29			37.3	
5:40			37.4	Heating pad turned off
5:45			37.4	Slight Traube-Hering waves in blood pressure tracing; heating pad turned to "low"
5:50				8 cc. of sedimented red blood cells injected into femoral vein
6:00			37.3	Traube-Hering waves almost imperceptible
6:14				5 cc. of sedimented red blood cells injected into femoral vein
6:15			37.4	
6:25			37.3	
6:27				5 cc. of sedimented red blood cells injected into femoral vein
6:30			37.3	Traube-Hering waves present
6:33				Traube-Hering waves gone
6:36				Hematocrit sample no. 2 taken from femoral artery
6:43				Animal killed

Hematocrit sample no. 1 (before artificial circulation), 50 per cent cells.

Hematocrit sample no. 2, no hemolysis of plasma; 27 per cent cells.

Autopsy.—There was a small hematoma in the superior mediastinum. Both lungs were expanded and pink and floated in water. There were no purpuric spots on the surface of the lungs or on cross-section. Microscopic examination of a section of the lower lobe of the right lung showed a few minute areas of atelectasis.

There was no pulmonary edema. The heart was normal in appearance externally and on cross-section, except for an ecchymotic spot about 1 cm. in diameter on the anterior surface of the heart overlying the interventricular septum near the base. One coronary artery lay directly in the middle of this area. The artery was opened for a distance of 2 cm. No embolus was present. On cross-section this area appeared to be a subepicardial hemorrhage and did not extend into the myocardium. A section of the left ventricular wall through this area was examined microscopically. There was a small hemorrhage beneath the epicardium and in the very superficial portion of the myocardium about the coronary artery and its accompanying veins. There was no embolism or thrombosis of the vessels. No fragmentation or evidence of injury to cardiac muscle fibers was seen.

Experiments with Sterile Technic.—To discover whether the passage of blood through the artificial circuit produced any injurious after-effects on an animal, the following experiment was performed under sterile conditions in order to permit a prolonged survival period. Seventy per cent alcohol was circulated through the pumps, tubing and oxygenator for thirty minutes. The pumps and oxygenator were then thoroughly rinsed with 4 liters of sterile physiologic solution of sodium chloride and filled with a sterile solution of acacia. A small catheter was introduced into the trachea through the mouth, and anesthesia was maintained by ether vapor through the catheter. The chest was not opened. The right jugular vein and femoral artery were exposed through small incisions, and cannulas were introduced in the usual manner. Seventy-two milligrams of heparin per kilogram of body weight was given intravenously. The cannulas were then connected with the artificial circuit, and blood was withdrawn from the jugular vein and reinjected into the femoral artery, at a rate varying from 150 to 200 cc. per minute. Passage of blood through the artificial circuit at this rate was continued for one hour, after which the cannulas were removed and the vessels ligated. The wounds were then sutured. A sample of blood withdrawn at the end of the experiment contained 28 per cent cells and showed slight hemolysis. Recovery was uneventful except for the development of hematoma in both wounds. Five days later there was evidence of infection in the wounds, and the animal was killed. Blood obtained at autopsy was not hemolyzed, and no organisms were grown on culture. Thus it is possible to operate on an animal and render the blood incoagulable by the administration of heparin without causing a fatal hemorrhage from the operative wounds. The experiment also demonstrated that an animal can live for five days after its blood has been passed through the artificial circuit for a period of an hour.

Several attempts were made under sterile conditions to perform the entire experimental procedure of occluding the pulmonary artery, maintaining life by artificial circulation and then releasing the pulmonary artery and allowing the animal to recover. Fifteen such attempts were made unsuccessfully. In addition to the difficulties encountered in per-

forming the experiments under aseptic conditions, two other major complicating factors were present. One was the fact that the procedure was too long and too shocking to be entirely completed in one stage, so that in the majority of these fifteen experiments a preliminary operation was performed. The fourth rib and costal cartilage were resected, the pericardium was opened over the pulmonary artery and the cut edges of the pericardium were sutured to the pectoralis minor and intercostal muscles about the opening in the wall of the chest. The pectoralis major muscle and the skin were then closed over the pulmonary artery. After an interval of about two weeks the experiments were performed as has been described. The old incision was reopened, and the pulmonary artery was immediately exposed beneath the pectoralis major muscle. Occasionally infection prevented the performance of the second stage. At other times a dense plaque of scar tissue was found overlying the pulmonary artery, adherent to it and to the opening in the wall of the chest. In these instances an adequate exposure of the pulmonary artery could be obtained only by a tedious, time-consuming and hazardous dissection.

The other major difficulty encountered was that of anesthesia. Sodium barbital (0.45 Gm. per kilogram of body weight) injected intraperitoneally in the nonsterile experiments always produced prolonged narcosis and a lowering of the blood pressure. Both these effects were undesirable in the sterile survival experiments. Reduction of the amount of barbital resulted in inadequate surgical anesthesia. For these reasons ether was used in the sterile experiments, as it did not lower the blood pressure and the cats recovered consciousness a short time after the inhalation of ether vapor was stopped. The use of an inhalation anesthetic increased the difficulties of the experimental procedure because anesthesia could not be maintained in the ordinary manner when the pulmonary artery was completely occluded. While the pulmonary artery was occluded, ether vapor was circulated through the oxygenator in order to maintain anesthesia. The following technic was employed: During the operative procedures anesthesia was maintained by ether entering the lungs through an intratracheal catheter passed between the vocal cords with the aid of a laryngoscope. As the pulmonary artery was gradually occluded by the clamp, the amount of ether vapor entering the tracheal catheter was reduced, and ether vapor was added in increasing amounts to the oxygen and carbon dioxide mixture entering the oxygenator. Finally, the administration of ether by the intratracheal catheter was discontinued entirely, and anesthesia was maintained by ether vapor in the oxygenator. When the pulmonary artery was released, the reverse procedure was carried out. This double administration of ether required the undivided attention of one person throughout the experiment.

That the entire procedure can be successfully carried through with the animal under ether anesthesia was shown by experiment 64. This experiment was not sterile, but the technic was otherwise similar to that used in the sterile experiments, and ether anesthesia was employed throughout. The pulmonary artery was completely occluded for thirty minutes, during which time life was maintained by the artificial circulation. The artificial circulation was continued at a reduced volume flow for fifty-three minutes after the pulmonary artery was released. It was then stopped. The cannulas were removed from the femoral artery and the jugular vein. These vessels were ligated, and the wounds were closed. The wound in the chest was also closed after the clamp was removed from the pulmonary artery. The animal died two hours after the artificial circulation was stopped. The respiratory rate became increasingly rapid before death. Autopsy showed bilateral pneumothorax and practically complete collapse of both lungs. However, the animal apparently recovered consciousness after the ether anesthesia was stopped. All four limbs and the head were moved, and the animal made several attempts to stand up.

COMMENT

There are several features of the apparatus and method which could be improved on. For example, all the experiments were performed in the presence of marked acute anemia. Hematocrit readings were made at the conclusion of twenty-seven experiments. The percentage of cells varied between 4 and 29, the median value being 13.5 per cent. This anemia resulted from dilution of the animal's blood with the solution of acacia in the artificial circuit. The dilution was avoided in a few experiments by filling the pumps and tubing with blood from one or more cats. The dilution might also be diminished by further reducing the fluid capacity of the pumps, tubing and oxygenator. During the course of these experiments the volume of the pumps and tubing was reduced from an initial 130 cc. to a final 41 cc. Any further reduction in volume would entail a relatively large increase in the velocity of the blood with an increase in trauma and hemolysis. However, the volume of fluid required in the pumps and tubing could probably be reduced by simplification in design. It is not possible to make any significant reduction in the volume of blood required in the oxygenator. Here again a different design might accomplish the purpose. The success obtained despite the severe anemia seems to indicate that the circulation might be maintained with relative ease if the anemia were avoided, provided the blood was still adequately oxygenated.

There was some difficulty in avoiding hemolysis. At times this was due to inadequate rinsing of the pumps and oxygenator with physio-

logic solution of sodium chloride. In twenty-six experiments the degree of hemolysis was noted. It varied from none to 40 per cent. The latter figure refers to the color on a Tallqvist hemoglobin scale to which the color of the plasma most nearly compared. The hemolysis of 40 per cent occurred immediately after a marked reduction in size of the glass and rubber tubing composing the artificial circuit. It was reduced to less than 10 per cent by the use of larger tubing where the flow of blood was most rapid, that is, between the blood valves of each pump where the flow was completely intermittent. Avoidance of sharp changes in direction of the blood stream was also thought to decrease trauma and hemolysis.

Heparin was used as an anticoagulant. A dose sufficient to render all the blood incoagulable was given. In one experiment (described previously) in which the animal survived for five days, a single dose of 350 mg. of heparin was given to a cat weighing 4.9 Kg. Gross¹⁷ has shown that heparin given intravenously produces an immediate increase in clotting time. The rate of return to normal is rapid at first and then slower. He noted that the effect of heparin in rabbits tended to vary directly with the dose. In one experiment 10 mg. of heparin was injected in a rabbit weighing 1.7 Kg. A return to the normal clotting time began in twenty minutes and was complete in one and a half hours. Howell¹⁸ has shown that when enough heparin has been used to make all of an animal's blood incoagulable the coagulation time returns to normal in three hours. In a dog weighing 13½ pounds (6 Kg.), enough heparin to render the blood incoagulable was injected daily for six days, without noticeable effect on the red or white cells, platelet count or clotting time twenty-four hours after each injection.¹⁹ With a purified preparation of heparin, ten transfusions of blood have been given in man, with slight reactions in two instances.¹⁸

In twenty-one experiments the pulmonary artery was completely occluded for fifteen minutes or more. In only one of these experiments was the occlusion maintained for more than an hour. In this instance respirations continued for two hours and fifty-one minutes with the pulmonary artery completely occluded. In all the other experiments it was possible to maintain the occlusion of the pulmonary artery for only an hour or less. A frequent cause of failure to maintain the occlusion for longer periods was some defect in the apparatus. In the others, however, a gradual decrease occurred in the amount of venous blood

17. Gross, P.: Duration of Anticoagulant Action of Heparin in Vivo in Relation to Dosage, *Proc. Soc. Exper. Biol. & Med.* **26**:383, 1929.

18. Howell, W. H.: The Purification of Heparin and Its Chemical and Physiological Reactions, *Bull. Johns Hopkins Hosp.* **42**:199, 1928.

19. Howell, W. H., and McDonald, C. H.: Note on the Effect of Repeated Intravascular Injections of Heparin, *Bull. Johns Hopkins Hosp.* **46**:365, 1930.

which could be withdrawn without sucking the venous wall into the tip of the cannula. This probably indicated a decreased venous return to the heart, which was not due to a failure of respiration because the respiratory movements were almost invariably deeper than normal. It may have been due to the gradual loss of fluid from the blood into the tissues. This seems a likely explanation, although the blood pressure was generally maintained above the level which is associated with the development of shock. The increased depth of the respiratory movements would seem to indicate an insufficient supply of oxygen to both the capillaries and the tissues. Lack of oxygen increases permeability of the capillaries,²⁰ and this in turn might account for loss of fluid from the blood. In most experiments there was probably an adequate saturation of the arterial blood with oxygen, but there was always a severe acute anemia, and the volume flow of blood may not have been adequate to compensate for this. The reversal of the flow of blood in the abdominal and the thoracic aorta may have been a contributing factor, because the branches now formed acute angles with the direction of the flow of blood instead of angles between 90 and 180 degrees. From simple principles of hydraulics, this would result in a diminished flow of blood through these branches. This argument would apply to the abdominal viscera but not to the branches on the arch of the aorta supplying the head and upper extremities. However, no hemorrhages or edema were observed at autopsy in the abdominal viscera on gross examination. Finally, there is another possible cause of the gradually diminishing venous return. There is a possibility that very minute bubbles of oxygen were drawn into the lower arterial blood pump and then physically dissolved in the plasma by the high pressure developed in the tubing leading to the arterial cannula. With a return to the lower pressure in the animal's vessels the bubbles of oxygen might reform and thus block the systemic capillaries.

There was undoubtedly an excessive loss of water vapor from the blood during its passage through the oxygenator. In the experiment in which the occlusion was maintained for two hours and fifty minutes, the mixture of oxygen and carbon dioxide was warmed to 37 C. and saturated with water vapor before being passed through the oxygenator. The water vapor, however, condensed on the cool copper tube leading through the stationary cylinder of the oxygenator and dripped into the blood. There was excessive hemolysis in this experiment which must have been partly due to this factor. The rate of condensation under similar conditions was determined the following day. Water was found

20. Landis, E. M.: Micro-Injection Studies on Capillary Permeability: III. The Effect of Lack of Oxygen on the Permeability of the Capillary Wall to Fluid and to the Plasma Proteins, *Am. J. Physiol.* **83**:528, 1928.

to drip from the copper tube at the rate of 23 cc. an hour. As blood passed through the artificial circuit for over three hours, more than 70 cc. of water must have been introduced into the circulation by this means. No further attempts were made to saturate the gas entering the oxygenator with water vapor, although this probably should have been done and the condensation avoided by warming the metal tube.

Various types of apparatus have been designed for perfusion of isolated organs and even whole animals. So far as I am aware there has been no report of a successful temporary substitution of an entirely mechanical apparatus for the heart and lungs of an animal. Lindbergh²¹ has described an apparatus for the prolonged sterile perfusion of isolated organs. Gibbs²² has devised an artificial heart for use in cats and dogs which has proved helpful in the investigation of pharmacologic problems.²³ The artificial heart is connected to the great vessels within the pericardium, and the blood is oxygenated in the animal's own lungs. Barcroft²⁴ carried out successful perfusion of a dog by tying cannulas in the aorta and great veins and circulating the blood by means of a centrifuge pump. The blood was oxygenated by passing it through a heart lung preparation of another dog.

None of these methods could be employed in the solution of our problem. Our object was to determine whether the circulation could be temporarily aided by mechanical means in the presence of an obstruction of the pulmonary artery. This temporary mechanical aid was necessarily of such nature as not to interfere with the ultimate survival of the animal. The withdrawal and reinjection of blood had to be accomplished through peripheral vessels of such size that the loss of their continuity by ligation would entail no serious ultimate consequences.

SUMMARY

The object of these experiments was to determine whether the circulation could be aided by artificial means in the presence of partial or complete occlusion of the pulmonary artery. The means employed were the withdrawal of blood from a peripheral vein, the introduction of oxygen into that blood and the reinjection of the blood into a peripheral artery in a central direction. The blood was thus short circuited around the obstruction in the pulmonary artery, and a part or all of the work

21. Lindbergh, C. A.: An Apparatus for the Culture of Whole Organs, *J. Exper. Med.* **62**:409, 1935.

22. Gibbs, O. S.: An Artificial Heart, *J. Pharmacol. & Exper. Therap.* **38**: 197, 1930; Artificial Heart for Dogs, *ibid.* **49**:181, 1933.

23. Tainter, M. L.: Use of the Gibbs Artificial Heart in the Study of Circulatory Phenomena, *Arch. internat. de pharmacodyn. et de therap.* **42**:186, 1931.

24. Barcroft, H.: Observations on the Pumping Action of the Heart, *J. Physiol.* **78**:186, 1933.

of the heart and lungs was temporarily taken over by artificial means. This mechanical aid to the circulation in the presence of a partial or complete occlusion of the pulmonary artery has been satisfactorily demonstrated. Because of the necessity for employing a sterile technic, the ability of an animal to recover for more than a few hours from complete occlusion of the pulmonary artery has not been demonstrated. Further improvement and simplification of the apparatus and technic are probably necessary before successful results with a sterile technic can be obtained.

CONCLUSIONS

1. Short circuiting blood around a partial obstruction in the pulmonary artery by means of a perfusion apparatus aids in maintaining the blood pressure and respiration.
2. Life can be maintained for short periods of time in the presence of complete obstruction of the pulmonary artery by a perfusion method which does not involve damage to the great vessels of the body.
3. The normal circulation and respiration can be spontaneously reestablished and maintained for several hours after a thirty minute period of complete occlusion of the pulmonary artery.

EFFECT OF VAGOTOMY ON THE GASTRIC MOTOR MECHANISM OF MAN

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The influence of the vagus nerve on the gastric motor mechanism has inspired extensive investigation; nevertheless, diversity of opinion concerning its precise effect on the human stomach still exists. As a result, vague and paradoxical functions have been suggested. Apparent discrepancies are due in part to the infrequency of direct observations on man. These, however, are being gradually eliminated through the recent controlled investigations of human gastric function.

The wider recognition of indications for indirect or physiologic surgical treatment has increased the number of opportunities for the study of the neurogenic control of human function. During recent years attempts have been made to ameliorate certain abnormal states by the extirpation of organs related physiologically to the nature of the fundamental disease. Although these surgical procedures have been instituted primarily for their therapeutic effect, nevertheless, they have provided opportunities for the investigation of the physiologic properties of these organs. Thus, bilateral resection of the splanchnic nerves for the relief of juvenile diabetes¹ made possible observations on one phase of the nervous control of the human stomach. The results of our own studies in this field have already been reported.²

Presented before the Forty-Eighth Annual Meeting of the American Physiological Society, Washington, D. C., March 26, 1936.

From the Department of Surgery, Yale University School of Medicine and the Department of Medical and Surgical Research, Ohio State University.

1. de Takáts, Géza, and Fenn, G. K.: Bilateral Splanchnic Nerve Section in a Juvenile Diabetic, *Ann. Int. Med.* **7**:422 (Oct.) 1933. de Takáts, Géza; Fenn, G. K., and Trump, Ruth A.: Splanchnic Nerve Section in Juvenile Diabetes, *ibid.* **7**:1201 (April) 1934.

2. Barron, Louis E.; Curtis, George M., and Haverfield, William T.: The Effect of Bilateral Resection of the Splanchnic Nerves on Gastric Motility in Man, *Arch. Surg.* **32**:577 (April) 1936.

A further analysis of the effect of the extrinsic innervation on the gastric motor mechanism of man became possible when abdominal vagotomy was accomplished in the course of the management of a patient with vagotonia, a symptom complex described by Eppinger and Hess.³ In addition to the usual clinical studies, observations were made on the motor activities of the stomach before and after resection of the left abdominal vagus nerve and also during the therapeutic administration of atropine. The purpose of this paper is to report these results.

The present investigation was made possible through the cooperation of Dr. Bruce K. Wiseman, of the Medical Division of the Department of Medical and Surgical Research, Ohio State University. The diagnosis was made by him after a thorough investigation for more than a year.⁴ During this period various medical measures were employed in an attempt to control the condition. It was found that large doses of atropine produced definite symptomatic relief. Untoward by-effects of this treatment, however, were pronounced, and vagotomy was finally advised in an effort to relieve permanently the abdominal distress and attendant symptomatology. The preliminary and subsequent studies have demonstrated that many symptoms were the result of perverted physiologic gastro-intestinal activities. The clinical syndrome of vagotonia with the medical management pertaining to this patient is to be reported elsewhere by Dr. Wiseman.

HISTORICAL BACKGROUND

Because of certain physiologic implications, surgical interference with the extrinsic nerve supply to the human stomach has been advised and accomplished since 1899 for many organic and functional gastric abnormalities. Jaboulay⁵ was one of the first to extirpate the celiac plexus. Exner⁶ performed subdiaphragmatic resection of the vagus nerve in the management of tabetic crises. Postoperatively he observed gastric dilatation, atony and pylorospasm. Because of this he proposed gastrostomy or gastrojejunostomy.

Bircher⁷ performed vagotomy for the control of ulcer. He reported a subsequent disappearance of many distressing epigastric symptoms, associated with a reduction in the gastric secretion and acidity. In the

3. Eppinger, H., and Hess, L.: *Vagotonia, Nervous and Mental Disease Monograph 20*, New York, Nervous and Mental Disease Publishing Company, 1917.

4. Wiseman, Bruce K.: Personal communication to the authors.

5. Jaboulay: *Zentralbl. f. Chir.* 28:227, 1901; cited by McCrea.¹²

6. Exner, A.: *Tabische Krisen, Ulcus ventriculi und Vagus*, Wien, klin. Wchnschr. 25:1405, 1912. Exner, A., and Schwarzman, E.: *Gastrische Krisen und Vagotomie*, Mitt. a. d. Grenzgeb. d. Med. u. Chir. 28:15, 1914.

7. Bircher: *Arch. d. mal. de l'app. digestif* 11:135, 1921; cited by McCrea.¹³

management of certain gastric disorders, Latarjet⁸ recommended resection of all the extrinsic nerves in order to decrease the frequency and intensity of the gastric contractions. He reported that this operation was most suitable for patients with vagotonia in whom there was no gastric lesion.

The importance of the nervous element in the etiology of gastroduodenal ulcer was emphasized by Schiassi.⁹ He concluded that rest to the stomach and duodenum was of paramount importance and that this could be accomplished by gastroduodenal denervation, supplemented, if necessary, by gastro-enterostomy. Schiassi's operation was virtually a circumcision in the pyloric region. He reported excellent results.

Other investigators were less optimistic. Steinthal¹⁰ performed vagotomy on two patients with gastric ulcer and reported that the motility of the stomach was not influenced. He maintained that this operative procedure was ineffective in influencing ulcers situated high on the lesser curvature. Borchers¹¹ did not recommend section of the vagus nerve in order to influence reflex spasm and hypermotility because he did not regard the vagus as a true motor nerve. Best and Orator¹² advised against section of the nerve for the treatment of peptic ulcer.

McCrea¹³ and Laignel-Lavastine¹⁴ presented a more favorable outlook for this procedure. McCrea pointed out that organic stricture of the esophagus was one of the chief contraindications. Stenosis of the pylorus could be benefited most by other surgical procedures. Another more theoretical contraindication is that after gastric denervation visceral sensation may be abolished. In the absence of this protective mechanism, a serious lesion such as carcinoma of the stomach may develop silently. An analogous syndrome has been reported by Latarjet.⁸

8. Latarjet, A.: Résection des nerfs de l'estomac: Technique opératoire; résultats cliniques, *Bull. Acad. de méd., Paris* **87**:681, 1922. Latarjet, A., and Wertheimer, P.: Denervation of the Stomach, *Presse méd.* **31**:993, 1923.

9. Schiassi, Benedetto: The Rôle of the Pyloro-Duodenal Nerve Supply in the Surgery of Duodenal Ulcer, *Ann. Surg.* **81**:939, 1925.

10. Steinthal, C.: Blocking of the Sympathetic and Vagus Nerves, *Zentralbl. f. Chir.* **47**:1293, 1920; cited by McCrea.¹³

11. Borchers, E.: Motilitätsstörungen des Magens und Vagus Resektion, *Zentralbl. f. Chir.* **47**:1535, 1920.

12. Best, Russel R., and Orator, Victor: The Vagus Nerve and Its Relation to Peptic Ulcer, *Ann. Surg.* **96**:184, 1932.

13. McCrea, E. D.: The Nerves of the Stomach and Their Relation to Surgery, *Brit. J. Surg.* **13**:621, 1925.

14. Laignel-Lavastine: L'étude du sympathique et son intérêt chirurgical, *Rev. de chir.* **62**:663, 1924.

SURGICAL ANATOMY

Detailed descriptions of the anatomic relationship between the vagus nerve and the stomach have been published elsewhere.¹⁵ In brief, the nerve passes from the neck into the thorax and to the esophagus, there forming the so-called esophageal plexus (fig. 1). From this there arise two main trunks, an anterior and a posterior trunk (fig. 2). The anterior trunk passes downward through the diaphragm along the lesser curvature of the stomach. McCrea¹⁵ reported that the pylorus is innervated by the hepatic branch of the anterior trunk of the vagus

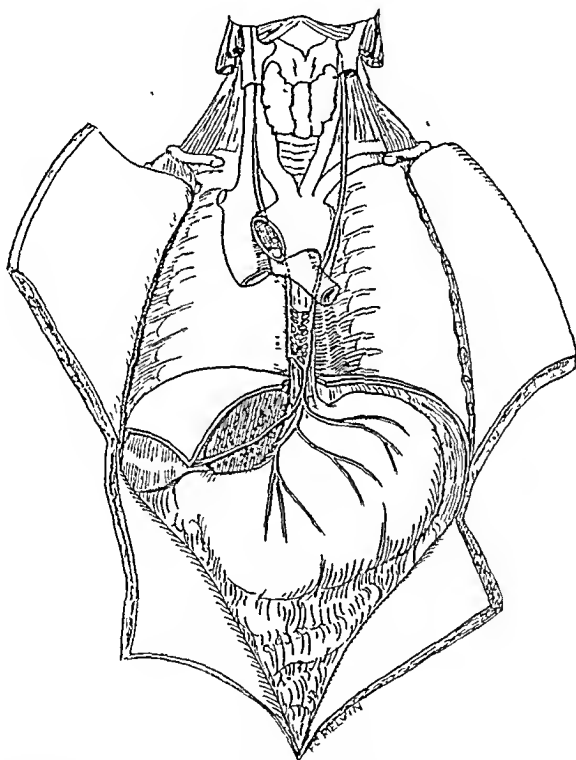


Fig. 1.—Drawing from an anatomic preparation showing the formation of the esophageal plexus.

nerve. The posterior trunk sends branches to the posterior surface of the stomach and to the pancreas, spleen, kidneys and small intestine.

Prior to vagotomy dissections were made in the anatomic laboratory in order to ascertain the relationship of the vagus nerve to the stomach and the neighboring viscera. Anterior (left) abdominal vagotomy was then accomplished on May 7, 1935, on our patient. The previous anatomic studies revealed that the best surgical approach to this nerve in the

15. (a) McCrea, E. D.: The Abdominal Distribution of the Vagus, *J. Anat.* 59:18, 1924. (b) McCrea.¹³

region of the cardia was through a high left rectus-splitting incision (fig. 3, insert). A thorough exploration at the time of the operation revealed the spleen, kidneys, adrenals, liver, gallbladder and large intestine to be normal. Complete examination of the stomach failed to disclose evidence of demonstrable disease. The stomach was then retracted downward, thus making the anterior trunk of the vagus nerve prominent to palpation (fig. 3). The nerve was identified and carefully dissected downward from the diaphragm to the cardia and along the lesser curvature. Care was taken not to injure the left gastric artery, which was in close proximity. A segment of the vagus nerve, about 3 cm., was then resected with its branches along the cardia. Because of the obvious

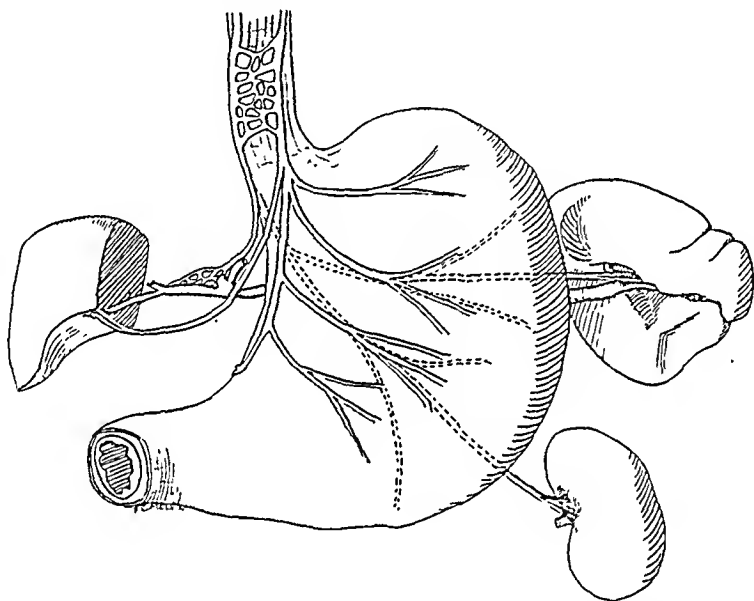


Fig. 2.—Drawing from an anatomic preparation showing the origin of the anterior and posterior trunks of the vagus nerve and their relationship to the stomach and the neighboring viscera.

anatomic difficulty in adequately exposing the posterior trunk of the nerve and because this branch of the nerve is considered to be of lesser physiologic significance,¹⁶ it did not seem prudent to subject the patient to the additional trauma necessitated by its resection. The wound was closed in the usual manner. The patient left the operating room in

16. (a) Bechterew and Mislowski: *Ztschr. f. klin. Med.* **29**:73, 1896; cited by McSwiney, B. A.: *Innervation of the Stomach*, *Physiol. Rev.* **11**:478, 1931. (b) Batelli, F.: *Action de diverses substances sur les mouvements de l'estomac et innervation de cet organe*, *Compt. rend. Acad. d. sc.* **122**:1568, 1896. (c) May, W. P.: *The Innervation of the Sphincters and Musculature of the Stomach*, *J. Physiol.* **31**:260, 1904.

good condition. Contrary to the findings of Exner,⁶ we did not observe any evidence of gastric atony or of dilatation occurring as an immediate or remote complication.

METHODS OF INVESTIGATING GASTRIC MOTILITY

The gastric motor mechanism was investigated by the balloon and kymographic method. As a preliminary measure, a balloon coated with barium sulfate and attached to a narrow rubber tube was swallowed. Roentgenologic visualization² of the balloon in the stomach made it possible to determine the accurate distance from this position to the incisor teeth. This was 50 cm. The tube was kept in this

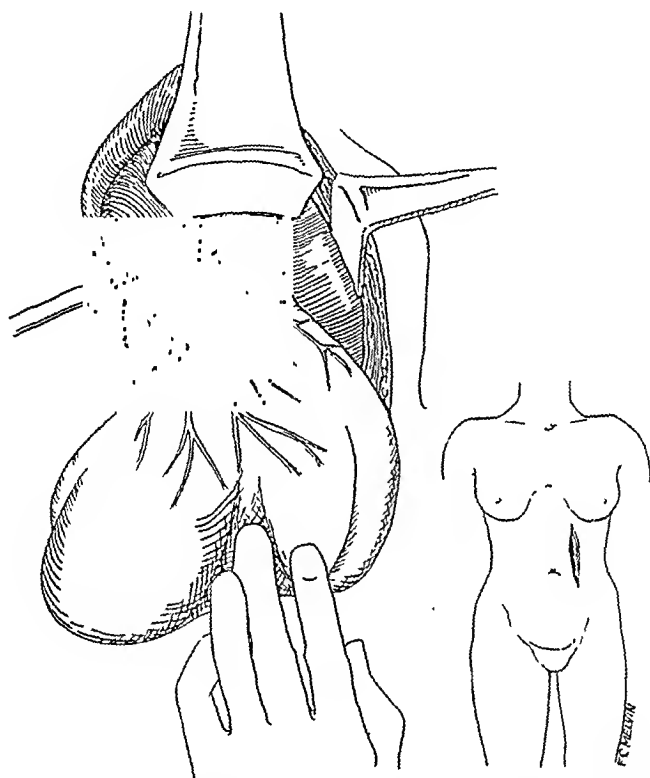


Fig. 3.—Drawing demonstrating the method of isolating the anterior trunk of the vagus nerve. By downward traction on the stomach, the nerve can be identified easily. The insert demonstrates the abdominal incision through which anterior abdominal vagotomy can be best accomplished.

position throughout each observation. Studies were made in the morning, about fourteen hours after the preceding meal. The details concerning the apparatus and the criteria employed in the evaluation of gastric motility have been described in a previous communication.²

The usual duration of each period of observation was approximately five hours. Thirteen experiments were made during the control period (table 1). After this the patient was given atropine, the dose of which varied with the character of the symptoms. The average dose was 75 minims (4.6 cc.) daily of the tincture of belladonna. Occasionally it was necessary to increase the dose. Nine observations

were made during this medication (table 2). Anterior (left) abdominal vagotomy was then performed. Studies of the gastric motility were resumed about a week later, and twelve subsequent observations were made (table 3). This patient returned to the hospital about five months after vagotomy for reinvestigation. Seven experimental observations were made at that time (table 4).

Accompanying these studies, observations were made on the emptying time of the stomach (table 5). The patient was given a test meal consisting of 3 ounces (93 Gm.) of Cream of Wheat, 2 ounces (62 Gm.) of barium sulfate and sufficient water to form a paste. As soon as the meal was eaten, fluoroscopy was performed to determine the gastric capacity. Fluoroscopic observations were then repeated at frequent intervals until barium was no longer evident in the stomach.

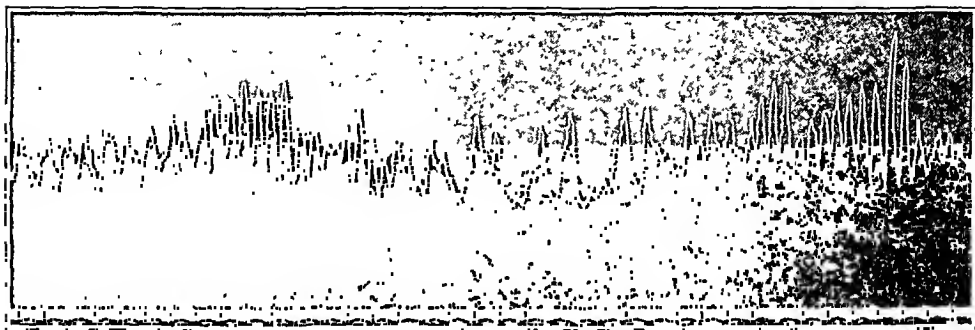


Fig. 4.—Kymographic tracing made on March 4, 1935, showing continuous gastric motility throughout an observation period of five hours and five minutes.

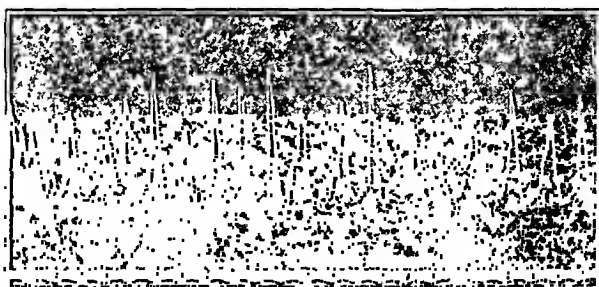


Fig. 5.—Tracing made on Feb. 25, 1935, showing a definite increase in the duration of periods of gastric motility. The total duration of this period was two hundred and sixty-seven minutes.

Attention was directed to the pylorus and to the body of the stomach in order to observe changes in tonus and contractility. Observations were made on the total emptying time, that is, the period from the time the test meal was eaten until it was seen no longer in the stomach. Owing to an occasional persistent coating of the walls of the stomach by barium, it was sometimes difficult to ascertain accurately when the stomach was completely empty, a difficulty also noted by other investigators.¹⁷ This artefact, however, was not constant.

17. McCrea, E. D.; McSwiney, B. A., and Stopford, J. S. B.: The Effect on the Stomach of Section of the Vagi Nerves, *Quart. J. Exper. Physiol.* **16**:195. 1926.

TABLE 1.—Analysis of Experiments on Gastric Motility During the Control Period*

Date of Experiment	Periods of Quiescence		Periods of Activity		Contractions					Comment
	Duration of Experiment	No.	Duration	No.	Type	Contractions			Amplitude	
						Continuous motility; type I and II contractions	Duration	Interval Between		
2/4/35	3 hr. 30 m.	1	34 m.	1	29 m.	I	Instestible	Max. 4.5 cm. Min. 1.5 cm.	Low grade	
2/11/35	1 hr. 5 m.	1	31 m.	1	31 m.	II	Instestible	Max. 4.5 cm. Min. 1.5 cm.		
2/21/35	5 hr. 15 m.	1	31 m.	1	31 m.	I	Instestible	Max. 4.5 cm. Min. 1.5 cm.	Low grade	
2/21/35	5 hr. 15 m.	1	31 m.	1	31 m.	II	Instestible	Max. 4.5 cm. Min. 1.5 cm.		
2/21/35	5 hr.	1	31 m.	1	31 m.	I	Instestible	Max. 4.5 cm. Min. 1.5 cm.	Low grade	
2/21/35	5 hr.	1	31 m.	1	31 m.	II	Instestible	Max. 4.5 cm. Min. 1.5 cm.		
2/25/35	5 hr. 35 m.	1	22 m.	1	48 m.	II	Instestible	Max. 4.5 cm. Min. 1.5 cm.	Low grade	
2/25/35	5 hr. 35 m.	1	22 m.	1	48 m.	II	Instestible	Max. 4.5 cm. Min. 1.5 cm.		
2/26/35	6 hr. 15 m.	1	54 m.	1	28 m.	II	Instestible	Max. 4.5 cm. Min. 1.5 cm.	Low grade	
2/26/35	6 hr. 15 m.	1	54 m.	1	28 m.	II	Instestible	Max. 4.5 cm. Min. 1.5 cm.		
3/1/35	5 hr. 5 m.	1	107 m.	1	41 m.	II	Instestible	Max. 4.5 cm. Min. 1.5 cm.	Low grade	
3/1/35	5 hr. 5 m.	1	107 m.	1	41 m.	II	Instestible	Max. 4.5 cm. Min. 1.5 cm.		
3/7/35	3 hr.	1	14 m.	1	42 m.	I	Instestible	Max. 4.5 cm. Min. 1.5 cm.	Low grade	
3/7/35	3 hr.	1	14 m.	1	42 m.	II	Instestible	Max. 4.5 cm. Min. 1.5 cm.		
3/8/35	3 hr.	1	98 m.	1	67 m.	II	Instestible	Max. 4.5 cm. Min. 1.5 cm.	Low grade	
3/11/35	5 hr.	1	37 m.	1	70 m.	I and II	Instestible	Max. 4.5 cm. Min. 1.5 cm.		
3/17/35	2 hr. 27 m.	1	49 m.	1	28 m.	I	Instestible	Max. 4.5 cm. Min. 1.5 cm.	Low grade	
3/17/35	2 hr. 27 m.	1	49 m.	1	28 m.	II	Instestible	Max. 4.5 cm. Min. 1.5 cm.		
3/20/35	5 hr.	1	14 m.	1	53 m.	I and II	Instestible	Max. 4.5 cm. Min. 1.5 cm.	Low grade	
3/20/35	5 hr.	1	14 m.	1	53 m.	II	Instestible	Max. 4.5 cm. Min. 1.5 cm.		
3/21/35	5 hr. 10 m.	1	64 m.	1	121 m.	II	Instestible	Max. 4.5 cm. Min. 1.5 cm.	Low grade	
3/21/35	5 hr. 10 m.	1	64 m.	1	121 m.	II	Instestible	Max. 4.5 cm. Min. 1.5 cm.		
3/21/35	5 hr. 10 m.	1	163 m.	1	30 m.	II	Instestible	Max. 4.5 cm. Min. 1.5 cm.	Low grade	
3/21/35	5 hr. 10 m.	1	163 m.	1	30 m.	II	Instestible	Max. 4.5 cm. Min. 1.5 cm.		
3/21/35	5 hr. 10 m.	1	163 m.	1	30 m.	II	Instestible	Max. 4.5 cm. Min. 1.5 cm.	Low grade	
3/21/35	5 hr. 10 m.	1	163 m.	1	30 m.	II	Instestible	Max. 4.5 cm. Min. 1.5 cm.		

in this table and in tables 2, 3 and 4, m. Indicates minutes; s., seconds; Min., minimum, and Max., maximum.

Observations on the emptying time of the stomach were made during an adequate control period, during the therapeutic administration of atropine and subsequent to anterior (left) abdominal vagotomy (table 5).

RESULTS WITH BALLOON METHOD

The results obtained during the preoperative control period are recorded in table 1. Intense gastric motility was a common observation. Occasionally this persisted throughout an entire period of observation (fig. 4). When a period of gastric quiescence was observed, it frequently was of short duration. In a few instances there were periods of quiescence lasting over one hundred minutes. However, the average duration of the periods of motility was definitely increased (fig. 5) in contrast to the duration of periods of quiescence.

Occasionally it was impossible to estimate accurately the number of, the duration of, and the interval between, contractions because of the rapidity with which they occurred. In the majority of instances definite objective measurements could be made. These are recorded in table 1.

A signal magnet and an electric key were incorporated into the system. The patient was instructed to indicate any abdominal pain by pressing the key. This made it possible to correlate by kymographic tracings any abdominal discomfort with the associated phase of gastric motility. Such a relationship was observed. During the control period severe contractions were noted, occasionally of sufficient magnitude to rupture the balloon (table 1). These contractions seemed to occur simultaneously with the epigastric distress.

Gastric tetany² was common. This too was accompanied by transitory discomfort, which practically always disappeared with the ensuing period of gastric quiescence. With the resumption of intense gastric motility, there was a simultaneous recurrence of epigastric distress.

The duration of periods of quiescence is recorded in table 1. The number of contractions during periods of motility, tabulated here, was definitely increased, probably because of the increase in the duration of periods of gastric motility. The amplitude of the contractions was also increased, occasionally to 7.5 and 8 cm. This too was not constant. Great variability existed. In general, there was a definite increase in gastric tonus as demonstrated by the balloon method.

After the control period the patient was given large doses of atropine, which varied with the symptoms manifested. Nine observations were made. The data are given in table 2.

During this medication the observations revealed a slight reduction in the intensity of the motor activities of the stomach. In many instances the contractions were low. Frequently weak fluctuations in gastric tonus (fig. 6) persisted throughout the period of observation. When tetany appeared, it was feeble and usually not accompanied by epigastric dis-

TABLE 2.—Analysis of Experiments on Gastric Motility During Medication with Atropine

Date of Experiment	Duration of Experiment	Periods of Quiescence		Periods of Activity		Contractions					Comment		
		No.	Duration	No.	Duration	Type	No.	Duration		Interval Between		Amplitude	
								Inestimable	Inestimable				Inestimable
1/17/35	5 hr.	1	95 m.	I	Inestimable	Inestimable	Inestimable	Inestimable	Inestimable	Max. 2.5 cm. Min. 1.5 cm.	Low grade motility throughout observation period
4/20/35	5 hr.	1	62 m.	1	62 m.	I	Inestimable	Inestimable	Inestimable	Inestimable	Inestimable	Max. 2.5 cm. Min. 1.5 cm.	
4/22/35	5 hr. 15 m.	1	42 m.	1	29 m.	I	Inestimable	Inestimable	Inestimable	Inestimable	Inestimable	Max. 1.6 cm. Min. 1.5 cm.	
4/25/35	4 hr. 35 m.	1	38 m.	1	38 m.	I	Inestimable	Inestimable	Inestimable	Inestimable	Inestimable	Max. 1.5 cm. Min. 1.0 cm.	
		Continuous low grade motility with fluctuations in gastric tone											
		1	29 m.	1	15 m.	II	Inestimable	Inestimable	Inestimable	Inestimable	Inestimable	Max. 1.0 cm. Min. 1.0 cm.	
4/27/35	4 hr. 23 m.	1	63 m.	1	92 m.	II	Inestimable	Inestimable	Inestimable	Inestimable	Inestimable	Max. 1.0 cm. Min. 1.0 cm.	
		1	46 m.	1	46 m.	II	Inestimable	Inestimable	Inestimable	Inestimable	Inestimable	Max. 1.0 cm. Min. 1.0 cm.	
		1	20 m.	I, II and III	Inestimable	Inestimable	Inestimable	Inestimable	Inestimable	Max. 1.0 cm. Min. 1.0 cm.	
		1	18 m.	1	56 m.	I, II and III	Inestimable	Inestimable	Inestimable	Inestimable	Inestimable	Max. 1.0 cm. Min. 1.0 cm.	
		1	35 m.	1	49 m.	II and III	Inestimable	Inestimable	Inestimable	Inestimable	Inestimable	Max. 1.0 cm. Min. 1.0 cm.	
		1	32 m.	1	31 m.	II	Inestimable	Inestimable	Inestimable	Inestimable	Inestimable	Max. 1.0 cm. Min. 1.0 cm.	
4/30/35	5 hr.	1	36 m.	II	Inestimable	Inestimable	Inestimable	Inestimable	Inestimable	Max. 1.0 cm. Min. 1.0 cm.	
		1	16 m.	1	34 m.	I, II and III	Inestimable	Inestimable	Inestimable	Inestimable	Inestimable	Max. 1.0 cm. Min. 1.0 cm.	
		1	14 m.	1	118 m.	II	Inestimable	Inestimable	Inestimable	Inestimable	Inestimable	Max. 1.0 cm. Min. 1.0 cm.	
		1	36 m.	1	26 m.	II	Inestimable	Inestimable	Inestimable	Inestimable	Inestimable	Max. 1.0 cm. Min. 1.0 cm.	
5/ 2/35	5 hr 23 m.	1	61 m.	I	Inestimable	Inestimable	Inestimable	Inestimable	Inestimable	Max. 1.0 cm. Min. 1.0 cm.	
		1	58 m.	1	30 m.	I	Inestimable	Inestimable	Inestimable	Inestimable	Inestimable	Max. 1.0 cm. Min. 1.0 cm.	
		1	64 m.	1	49 m.	II	Inestimable	Inestimable	Inestimable	Inestimable	Inestimable	Max. 1.0 cm. Min. 1.0 cm.	
		1	58 m.	1	49 m.	II	Inestimable	Inestimable	Inestimable	Inestimable	Inestimable	Max. 1.0 cm. Min. 1.0 cm.	
5/ 3/35	5 hr.	1	63 m.	I and II	Inestimable	Inestimable	Inestimable	Inestimable	Inestimable	Max. 1.0 cm. Min. 1.0 cm.	
		1	42 m.	1	60 m.	I and II	Inestimable	Inestimable	Inestimable	Inestimable	Inestimable	Max. 1.0 cm. Min. 1.0 cm.	
		1	37 m.	1	96 m.	II	Inestimable	Inestimable	Inestimable	Inestimable	Inestimable	Max. 1.0 cm. Min. 1.0 cm.	
		1	55 m.	II	Inestimable	Inestimable	Inestimable	Inestimable	Inestimable	Max. 1.0 cm. Min. 1.0 cm.	
		1	26 m.	1	103 m.	II	Inestimable	Inestimable	Inestimable	Inestimable	Inestimable	Max. 1.0 cm. Min. 1.0 cm.	
5/ 4/35	4 hr.	1	45 m.	1	11 m.	I	Inestimable	Inestimable	Inestimable	Inestimable	Inestimable	Max. 1.0 cm. Min. 1.0 cm.	
		Low grade motility											

Period terminated in tetany

tress. Although in some instances the contractions measured from 4 to 5 cm., in general there was a definite decrease in the amplitude. Associated with the slight decrease in gastric tonus, there was a moderate reduction in the number of contractions. The duration of the contractions remained unchanged, but there was a slight increase in the interval between contractions (fig. 7). Some symptomatic relief was experienced during the use of atropine.

After left abdominal vagotomy twelve experiments were made by the balloon method. The results are recorded in table 3. After vagotomy there ensued a definite decrease in the duration of periods of gastric

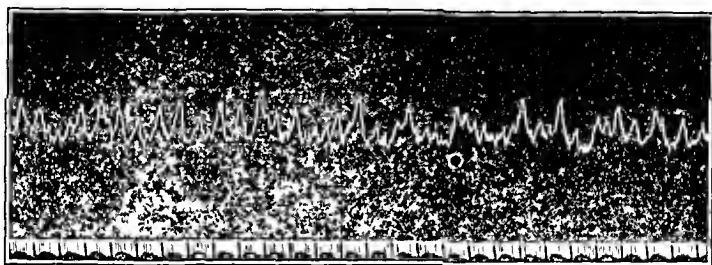


Fig. 6.—Tracing made on April 20, 1935, showing low grade motility with fluctuations in gastric tonus during intense medication with atropine.



Fig. 7.—Tracing made on May 4, 1935, showing an increase in the interval between contractions during intense medication with atropine.

motility (fig. 8). This in turn was associated with a corresponding increase in the duration of periods of quiescence (fig. 9). Frequently the motility was low grade and blended with weak fluctuations in gastric tonus. When contractions were observed, they were feeble (fig. 10).

The various criteria associated with the contractions are recorded in table 3. The number of contractions during each period of motility was decreased. Although the duration of the contractions remained essentially unchanged, there was an increase in the interval between contractions. In some instances this was nine and twelve minutes (fig. 11), in contrast to an approximate average of two minutes during

TABLE 3—Analysis of Experiments on Gastric Motility After Intuition (Left) Abdominal Tactotomy

Experiments on Gastric Motility After Infusion (Left) Abdominal Lapotomy											
Date of Experiment	Duration of Experiment	Periods of Quiescence		Periods of Activity		Type	Contractions		Interval between Contractions	Amplitude	Comments
		No	Duration	No	Duration		Max	Min			
5/23/35	5 hr 30 m	1	75 m	1	107 m	II	Max 1 m 10 s Min 1 s Min 0 s	21	Max 1 m 0 s Min 1 m 20 s Min 1 m	Max 1 cm Min 2 cm Min 3 cm Min 1.5 cm	Comm at interval between contractions was definitely increased. Approximate interval between contractions, about 2 m
5/27/35	3 hr 20 m	1	80 m	1	43 m	II	Max 75 s Min 0 s Min 1 s Min 0.5 s Min 0.5 s	19	Max 7 m Min 3 s Min 1 m 5 s Min 1 s Min 2 m 25 s Min 25 s	Max 1.5 cm Min 1 cm Min 1.5 cm Min 1.5 cm Min 1.5 cm Min 1.5 cm	Working interval between contractions, about 2 m
5/28/35	3 hr	1	96 m	1	31 m	II	Max 1 m Min 0.5 s Min 1 m Min 10 s	15	Max 6 m Min 6 s Min 7 m Min 1 m	Max 1.5 cm Min 2 cm Min 1.5 cm Min 2 m	Interval between contractions, about 2 m
5/29/35	5 hr	1	30 m	1	24 m	II	Max 1 m 1 s Min 1 m Min 10 s	11	Max 1 m 1 s Min 1 m Min 10 s	Max 1.5 cm Min 2 cm Min 1.5 cm Min 2 m	Interval between contractions, about 2 m
5/30/35	3 hr	1	53 m	1	33 m	I and II	Max 1 m 1 s Min 1 m Min 10 s	2	Max 1 m 1 s Min 1 m Min 10 s	Max 1.5 cm Min 2 cm Min 1.5 cm Min 2 m	Interval between contractions, about 2 m
6/24/35	3 hr	1	23 m	1	70 m	II	Max 75 s Min 10 s Min 1 m 10 s Min 10 s	27	Max 1 m 7 s Min 1 s Min 1 m Min 10 s	Max 2.5 cm Min 1 cm Min 1 cm Min 1.5 cm	Rhythmic contractions, about 2 m
6/25/35	Continuous low grade motility throughout the observation period	1	63 m	1	27 m	II	Max 75 s Min 10 s Min 1 m 10 s Min 10 s	20	Max 1 m 7 s Min 1 s Min 1 m Min 10 s	Max 2.5 cm Min 1 cm Min 1 cm Min 1.5 cm	Rhythmic contractions, about 2 m
6/26/35	3 hr	1	125 m	1	27 m	II	Max 75 s Min 10 s Min 1 m 10 s Min 10 s	37	Max 1 m 7 s Min 1 s Min 1 m Min 10 s	Max 2.5 cm Min 1 cm Min 1 cm Min 1.5 cm	Rhythmic contractions, about 2 m
6/27/35	3 hr	1	49 m	1	25 m	II	Max 75 s Min 10 s Min 1 m 10 s Min 10 s	27	Max 1 m 7 s Min 1 s Min 1 m Min 10 s	Max 2.5 cm Min 1 cm Min 1 cm Min 1.5 cm	Rhythmic contractions, about 2 m
6/28/35	3 hr	1	40 m	1	27 m	II	Max 75 s Min 10 s Min 1 m 10 s Min 10 s	27	Max 1 m 7 s Min 1 s Min 1 m Min 10 s	Max 2.5 cm Min 1 cm Min 1 cm Min 1.5 cm	Rhythmic contractions, about 2 m
6/29/35	3 hr 5 m	1	14 m	1	35 m	I and II	Max 75 s Min 10 s Min 1 m 10 s Min 10 s	20	Max 1 m 7 s Min 1 s Min 1 m Min 10 s	Max 2.5 cm Min 1 cm Min 1 cm Min 1.5 cm	Rhythmic contractions, about 2 m
6/29/35	3 hr 5 m	1	14 m	1	35 m	I and II	Max 75 s Min 10 s Min 1 m 10 s Min 10 s	20	Max 1 m 7 s Min 1 s Min 1 m Min 10 s	Max 2.5 cm Min 1 cm Min 1 cm Min 1.5 cm	Rhythmic contractions, about 2 m
6/29/35	3 hr 5 m	1	14 m	1	35 m	I and II	Max 75 s Min 10 s Min 1 m 10 s Min 10 s	20	Max 1 m 7 s Min 1 s Min 1 m Min 10 s	Max 2.5 cm Min 1 cm Min 1 cm Min 1.5 cm	Rhythmic contractions, about 2 m

Date of Experiment	Duration of Experiment	Quiescence		Activity		Contractions					Comment
		No.	Duration	No.	Duration	Type	No.	Duration	Interval Between	Amplitude	
9/21/35	3 hr.	1	41 m.	1	23 m.	II	14	Max. 1 m. Min. 10 s.	Max. 3 m. Min. 5 s.	Max. 4 cm. Min. 1.5 cm.	Period terminated in weak tetany
		1	108 m.	1	5 m.	II	5	Max. 35 s. Min. 10 s.	Max. 1 m. Min. 5 s.	Max. 2 cm. Min. 1.5 cm.	
9/23/35	5 hr. 5 m.	1	51 m.	II	35	Max. 1 m. Min. 5 s.	Max. 3 m. 10 s. Min. 5 s.	Max. 3 cm. Min. 1.5 cm.	Low amplitude
		1	69 m.	1	24 m.	II	16	Max. 50 s. Min. 5 s.	Max. 4 m. 10 s. Min. 5 s.	Max. 2.5 cm. Min. 1.5 cm.	
		1	42 m.	1	50 m.	II	26	Max. 45 s. Min. 10 s.	Max. 4 m. 10 s. Min. 10 s.	Max. 3 cm. Min. 1 cm.	
9/24/35	5 hr.	1	9 m.	II	Instestible	Instestible	Instestible	Low grade	Intense motility
		1	20 m.	1	39 m.	II	40	Max. 35 s. Min. 5 s.	Max. 25 s. Min. 5 s.	Max. 8 cm. Min. 2.5 cm.	
		1	112 m.	1	19 m.	II	20	Max. 15 s. Min. 5 s.	Max. 15 s. Min. 5 s.	Max. 5.5 cm. Min. 2.5 cm.	
9/26/35	5 hr. 5 m.	1	43 m.	II	40	Max. 50 s. Min. 20 s.	Max. 1 m. 20 s. Min. 10 s.	Max. 6.5 cm. Min. 1.5 cm.	Period terminated in weak tetany
		1	88 m.	1	8 s.	II	53	Max. 1 m. 5 s. Min. 15 s.	Max. 3 m. Min. 15 s.	Max. 4 cm. Min. 1 cm.	
		1	17 m.	1	16 m.	II	8	Max. 45 s. Min. 10 s.	Max. 2 m. 50 s. Min. 1 m.	Max. 4.5 cm. Min. 1.5 cm.	
9/27/35	5 hr.	1	14 m.	I and II	Instestible	Instestible	Instestible	Low grade	Period terminated in weak tetany
		1	17 m.	1	80 m.	II	26	Max. 45 s. Min. 5 s.	Max. 55 s. Min. 5 s.	Max. 4 cm. Min. 1 cm.	
		1	96 m.	1	26 m.	II	19	Max. 40 s. Min. 5 s.	Max. 1 m. 40 s. Min. 5 s.	Max. 3 cm. Min. 1.5 cm.	
10/3/35	5 hr.	1	35 m.	1	41 m.	II	25	Max. 55 s. Min. 10 s.	Max. 4 m. Min. 10 s.	Max. 3.5 cm. Min. 1.5 cm.	Patient complained of "gas pains"
		1	95 m.	1	26 m.	II	15	Max. 1 m. Min. 15 s.	Max. 4 m. 30 s. Min. 5 s.	Max. 3.5 cm. Min. 1 cm.	
		1	103 m.	1	21 m.	II	16	Max. 45 s. Min. 10 s.	Max. 4 m. 20 s. Min. 10 s.	Max. 3 cm. Min. 1 cm.	
10/5/35	5 hr.	1	25 m.	1	26 m.	II	14	Max. 40 s. Min. 5 s.	Max. 5 m. Min. 5 s.	Max. 3 cm. Min. 1 cm.	Low amplitude
		1	106 m.	1	40 m.	I	Instestible	Instestible	Instestible	Low grade	

the preoperative control period. Between the contractions low grade fluctuations in gastric tonus were observed. Many contractions were atypical and therefore could not be classified accurately. Some contractions measured 7 cm., but in general the amplitude was decreased.

This patient returned to the University Hospital about five months after left abdominal vagotomy for the investigation of the late results. These are tabulated in table 4. The data revealed that the changes in the gastric motility previously noted after vagotomy had persisted. The duration of periods of motility was still decreased (fig. 12). The gastric tonus remained low, and the duration of periods of quiescence was

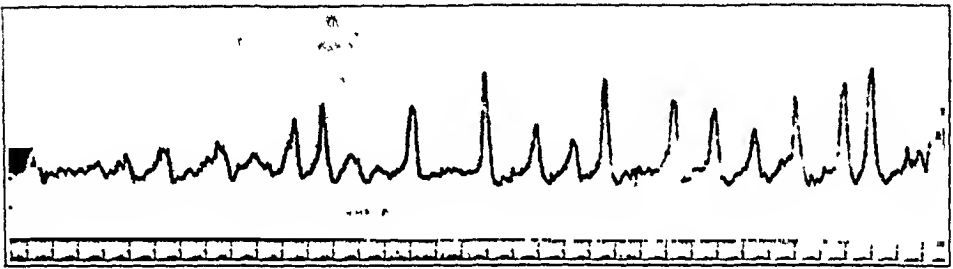


Fig. 8.—Tracing made on May 23, 1935, showing a decrease in the duration of periods of gastric motility after anterior (left) abdominal vagotomy. The total duration of this period was thirty minutes.

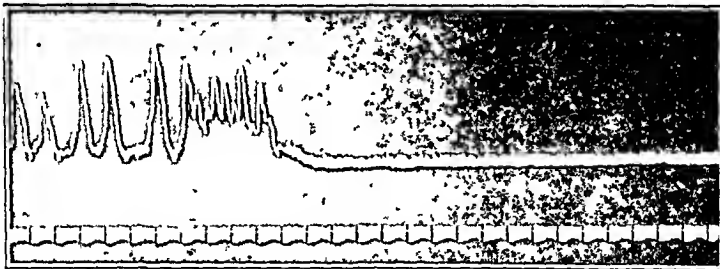


Fig. 9.—Tracing made on May 29, 1935, showing an increase in the duration of periods of gastric quiescence after anterior (left) abdominal vagotomy. The duration of this period was one hundred and seventeen minutes.

increased (fig. 13). The clinical status of the patient, however, was remarkably improved.

THE INFLUENCE OF ATROPINE AND OF VAGOTOMY ON THE EMPTYING TIME OF THE STOMACH

The studies on the total emptying time of the stomach revealed that during the control period there was increased peristaltic activity associated with a delay in the emptying time. This was attributed to spasticity of the pyloric sphincter. Four observations were made. The

results are recorded in table 5. There was some variability. The total emptying time ranged from five hours and thirty minutes to eight hours and averaged six hours and forty-nine minutes. The following is a typical protocol of one observation on the total emptying time made during the control period.

March 6, 1935, 7:30 a. m.: The test meal was eaten at this time.

7:40 a. m.: Except for a small gastric air bubble, the stomach appeared full. Active motility was noted. Deep contractions were observed passing over the stomach. No barium was seen in the duodenum.

8:00 a. m.: There was a slight decrease in the gastric contents. A few flecks of barium were seen in the duodenum. Deep constrictions in the stomach were noted.

9:00 a. m.: The stomach was estimated to be about one-half full. The remainder of the barium was distributed throughout the small intestine. Active peristalsis was observed.

TABLE 5.—*Influence of Atropine and of Anterior (Left) Abdominal Vagotomy on the Emptying Time of the Stomach*

Control Studies	During Medication with Atropine	After Vagotomy
7 hr., 45 min.	5 hr., 15 min.	2 hr., 30 min.
8 hr.	5 hr., 40 min.	2 hr., 45 min.
6 hr.	4 hr., 40 min.	3 hr., 15 min.
5 hr., 30 min.		
Av. 6 hr., 49 min.	Av. 5 hr., 12 min.	Av. 2 hr., 50 min. Five months after vagotomy, 2 hr.

10:15 a. m.: The stomach was estimated at this time to be about one-third full. The gastric contents were in the pyloric portion of the stomach. Considerable barium was seen in the small intestine but none in the large intestine.

11:30 a. m.: There was little change in the quantity of barium in the stomach. Peristalsis at this time was considerably weaker than previously observed.

12:45 p. m.: The stomach was estimated to be less than one-quarter full. The remainder of the barium was in the small intestine. There was active gastric peristalsis. No barium was seen in the large intestine.

2:30 p. m.: The stomach still contained a small amount of barium. The remainder of the barium was in the small intestine.

3:15 p. m.: A small amount of barium was still seen in the stomach; the remainder was in the small intestine.

3:30 p. m.: The stomach now contained no barium. The major portion was seen in the small intestine. Barium was observed in the ascending colon.

The total emptying time was eight hours.

During intense medication with atropine three observations were made (table 5). The results were fairly constant. The emptying time ranged from four hours and forty minutes to five hours and forty minutes and averaged five hours and twelve minutes. It would seem that this decrease in the emptying time of the stomach was due at least in part to a corresponding decrease in the spasticity of the pyloric

sphincter. The following is a typical protocol of an observation made during the medication with atropine.

April 24, 1935, 7.20 a. m.: The test meal was eaten at this time

7:30 a. m.: The stomach seemed practically full. A few flecks of barium were seen in the duodenum. Active peristalsis was seen passing over the stomach.

8:00 a. m.: The stomach was estimated to be about four-fifths full. The remainder of the barium was in the duodenum. Active gastric peristalsis was observed.

9:00 a. m.: The stomach was estimated to be about one-half full. The remainder of the barium was in the small intestine.

10:00 a. m.: The stomach appeared less than one-half full. Barium was distributed throughout the small intestine.

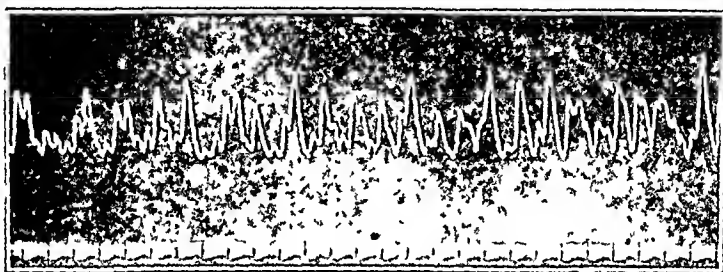


Fig. 10—Tracing made on May 28, 1935, showing low grade motility after anterior (left) abdominal vagotomy. The duration of this period was forty minutes.



Fig. 11.—Tracing made on May 21, 1935, showing a definite increase in the interval between contractions after anterior (left) abdominal vagotomy. On this day the interval between contractions was increased to twelve minutes and twenty seconds.

11:00 a. m.: The stomach was estimated to be about one-fourth full. The remainder of the barium was distributed throughout the small intestine. No barium was evident in the large intestine.

12:00 m.: The stomach contained a small amount of barium. The remainder of the barium was distributed throughout the small intestine. There was none in the large intestine.

12:30 p. m.: A few flecks of barium were seen in the stomach.

1:00 p. m.: The stomach now contained no barium. It was distributed throughout the small intestine.

The total emptying time was five hours and forty minutes.

After vagotomy the emptying time of the stomach was definitely decreased (table 5). It may seem paradoxical that a relatively hypomotile

stomach as determined by the gastrographic method should evacuate its contents with greater rapidity than during the hypermotile control period. However, in this untreated patient with vagotonia, it would seem that the hypermotility of the stomach was accompanied by marked pylorospasm. This would explain the abnormal retention of the gastric contents.

After left abdominal vagotomy, a patulous pylorus resulted. With each gastric contraction barium was observed passing through the pyloric sphincter, which appeared to be relaxed and relatively atonic, a phenomenon not observed during the control period. This pyloric

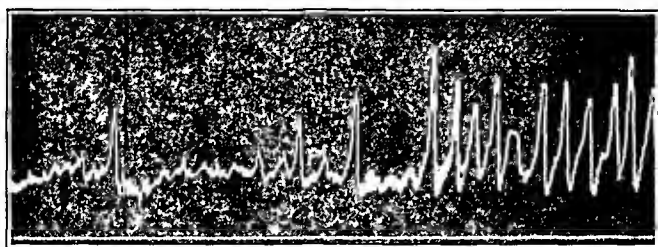


Fig. 12.—Tracing made on Oct. 21, 1935, five months after anterior (left) abdominal vagotomy, showing a persistent decrease in the duration of periods of gastric motility. The duration of this period was twenty-three minutes.

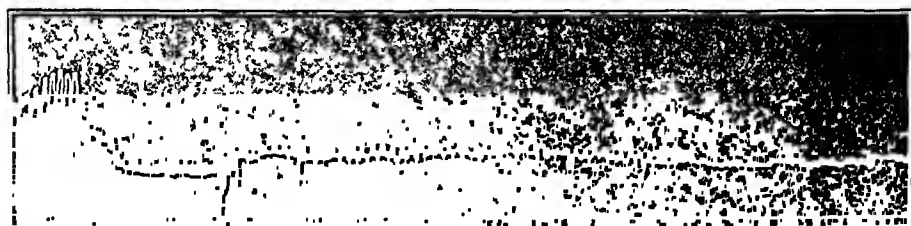


Fig. 13.—Tracing made on Oct. 21, 1935, five months after anterior (left) abdominal vagotomy, showing a persistent increase in the duration of periods of gastric quiescence. The duration of this period was one hundred and eight minutes.

relaxation we feel to be responsible, at least in part, for the decrease in the emptying time of the stomach.

Three observations were made after anterior (left) abdominal vagotomy. The emptying time ranged from two hours and thirty minutes to three hours and fifteen minutes. The average was two hours and fifty minutes, approximately four hours sooner than during the control period. The following is a typical protocol.

May 26, 1935, 7:30 a. m.: The test meal was eaten at this time.

7:45 a. m.: The stomach was estimated to be about four-fifths full. Occasionally deep contractions were observed. A few flecks of barium were seen in the duodenum.

8:00 a. m.: The stomach was estimated to be about half full. Moderate gastric peristalsis was observed. Barium was evident in the small intestine. With each contraction barium was seen passing into the duodenum.

8:30 a. m.: The stomach was estimated to be about one-third full. The remainder of the barium was in the small intestine.

9:00 a. m.: The stomach contained a small amount of barium which was in the pyloric antrum. No barium was seen in the large intestine.

9:30 a. m.: A small amount of barium was still seen in the stomach.

10:00 a. m.: Barium was no longer seen in the stomach. It was distributed throughout the small intestine.

The total emptying time was two hours and thirty minutes.

The following is a protocol of the emptying time of the stomach five months after vagotomy.

Oct. 5, 1935, 8:15 a. m.: The test meal was eaten at this time.

8:20 a. m.: The stomach was estimated to be about two-thirds full. A few flecks of barium were in the duodenum. Weak gastric peristalsis was noted.

8:45 a. m.: The stomach was estimated to be about one-fourth full. A few severe gastric contractions were seen. The barium was distributed throughout the small intestine.

9:45 a. m.: The stomach contained a small amount of barium. The remainder was distributed throughout the small intestine.

10:00 a. m.: The stomach contained a few flecks of barium. The remainder was distributed throughout the small intestine. Barium was not seen definitely in the large intestine.

10:15 a. m.: The stomach was empty. The barium was distributed throughout the small intestine.

The total emptying time was two hours.

COMMENT

Patients with vagotonia may manifest evidence of cardiospasm, gastric hypertonicity, hypermotility, pylorospasm and hyperacidity.¹⁸ These perverted physiologic activities can be verified by the gastrographic, roentgenographic and chemical methods. In our patient there was no evidence of cardiospasm, but gastric hypertonicity and hypermotility were common observations. Intense gastric motility was noted frequently throughout an observation period of five hours. Occasionally the contractions were of sufficient magnitude to rupture the balloon and force bromoform from the manometer. The amplitude of the contractions was definitely increased. This hypermotility was also demonstrable under the fluoroscope. Deep contractions were observed passing over a pylorus, which seemed to be in a constant spastic state.

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A relationship between the intense motility and the epigastric distress seemed evident. This was disclosed by the patient pressing an electric key which by means of a signal magnet produced an informative mark on the kymograph tracing. Conversely, epigastric distress disappeared when the stomach was quiescent.

Occasionally low grade motility occurred associated with fluctuations in gastric tonus. Since there is evidence¹⁹ to indicate that the vagus nerve may be both motor and inhibitory to the stomach, the reason for this variation is apparent. However, in spite of this, one can deduce from the literature and from the results presented here that the vagus nerve is the primary motor nerve to the human stomach.

Although cardiospasm was not observed in this patient, it nevertheless reflects the influence of the vagus nerve on the cardia. Openchowski²⁰ found that stimulation of the vagus nerve caused either contraction or relaxation and that the response was due to the frequency and the strength of the stimuli. Courtade and Guyon²¹ obtained a motor response and May^{10c} reported relaxation of the cardia followed by contraction. Occasionally he noted a pure motor response. Similar results were observed by Meltzer and Auer.²² Klee²³ and Koennecke²⁴ obtained closure of the cardia. Carlson, Boyd and Percy²⁵ found that although motor and inhibitory effects were possible, the response of the cardia depended on the tonus at the time of the stimulation of the vagus

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22. Meltzer, S. J., and Auer, J.: Vagus Reflexes upon the Oesophagus and Cardia, *Brit. M. J.* **2**:1806, 1906.

23. Klee, P.: Der Einfluss der Vagusreizung auf den Abbau der Verdauungsbewegungen. Röntgenversuche an der Rückenmarkskatze, *Arch. f. d. ges. Physiol.* **145**:557, 1912; Beiträge zur pathologischen Physiologie der Mageninnervation: II. Pylorusinsuffizienz und präpylorischer Gastropasmus, *Deutsches Arch. f. klin. Med.* **129**:275, 1920.

24. Koennecke, W.: Experimentelle Innervationsstörungen am Magen und Darm, *Ztschr. f. d. ges. exper. Med.* **28**:384, 1922.

25. Carlson, A. J.; Boyd, T. E., and Percy, J. F.: Studies on the Visceral Sensory Nervous System: XIII. The Innervation of the Cardia and Lower End of the Esophagus in Mammals, *Am. J. Physiol.* **61**:14, 1922; XIV. The Reflex Control of the Cardia and Lower Esophagus in Mammals, *Arch. Int. Med.* **30**: 409 (Oct.) 1922.

nerve. However, Caballero²⁶ maintained that stimulation of the nerve did not influence the cardiac sphincter.

Our observations on the untreated patient with vagotonia revealed hypertonicity and hypermotility of the stomach. Many gastrographic records exhibited a type of motility similar to that obtained after bilateral resection of the splanchnic nerves,²⁷ that is, when the stomach was under unopposed control of the vagus nerve. Occasionally low tonus with feeble motility was observed. This, however, was the exception rather than the rule.

It would seem that the occasional variability in the gastric motility observed during the control period and subsequent to vagotomy was due to the fact that the vagus nerve is both motor and inhibitory to the stomach. This was demonstrated by Langley¹⁹ and later confirmed by May.^{10c} Auer²⁷ showed in rabbits that only a slight degree of reflex inhibition occurred through the vagus nerve and that normal peristalsis was usually established after one or two days. He found that tracings from the pyloric third of the stomach exhibited no appreciable difference from those obtained from normal animals. Carlson, Boyd and Percy,²⁸ McCrea,¹³ and McCrea, McSwiney and Stopford²⁸ demonstrated that the response to stimulation was governed by the degree of gastric tonus present at the time of stimulation.

Van Braam Houckgeest²⁹ found that stimulation of the cervical vagus nerve caused contraction of the stomach. Klee²³ obtained only motor effects. Augmentation of peristalsis ensued with a moderately strong stimulus and tonic contraction with a strong stimulus. Bechterew and Mislowski^{10a} reported inhibition. They associated the response with the strength of the stimulus. Bercovitz and Rogers³⁰ and Bercovitz³¹ obtained preliminary contraction followed by relaxation. Can-

26. Caballero, R.: Étude expérimentale de la fermeture de l'extrémité inférieure de l'oesophage (épicaardia et cardia), *Compt. rend. Soc. de biol.* **87**:1359, 1922; Étude expérimentale de la fermeture de l'extrémité inférieure de l'oesophage, *ibid.* **88**:12, 1923.

27. Auer, J.: The Effect of Severing the Vagi or Splanchnics or Both upon Gastric Motility of Rabbits, *Am. J. Physiol.* **25**:334, 1910.

28. McCrea, E. D.; McSwiney, B. A., and Stopford, J. S. B.: The Effect on the Stomach of Stimulation of the Peripheral End of the Vagus, *Quart. J. Exper. Physiol.* **15**:201, 1925.

29. Van Braam Houckgeest, G.: *Arch. f. d. ges. Physiol.* **8**:163, 1874; cited by McSwiney.⁴⁹

30. Bercovitz, Z., and Rogers, F. T.: The Influence of the Vagi on Gastric Tonus and Motility in the Turtle, *Am. J. Physiol.* **55**:323, 1920. Rogers, F. T., and Bercovitz, Z.: The Rôle of the Intrinsic Plexuses in Determining the Effect on Gastric Motility of Vagus Stimulation, *ibid.* **56**:275, 1921.

31. Bercovitz, Z.: The Effect of Vagus Stimulation on Dog's Stomach, *Proc. Soc. Exper. Biol. & Med.* **19**:228, 1922.

non and Lieb³² also found that stimulation of the vagus nerve may inhibit the stomach. Daniélopou³³ observed that compression of the vagus nerve in the neck of man caused inhibition followed by augmented movements. Laughton³⁴ demonstrated in cats that stimulation of the dorsal vagus nucleus usually caused contractions, but inhibition also occurred if the tonus was high. According to Veach,³⁵ stimulation with a current of relatively low intensity caused a motor response of the stomach of a cat, while stimulation with a current of high frequency produced inhibition. McSwiney and Wadge³⁶ could not confirm this. They found that in a condition of low tonus stimulation of the vagus nerve with a current of low or high frequency caused contractions and increased the tonus. In a condition of high tonus, stimulation caused inhibition and relaxation.

The pylorospasm which seemed to be present during the untreated vagotonic state can also be explained on the basis of hyperirritability of the vagus nerve. Crisler and his associates,³⁷ who observed pylorospasm associated with anoxemia, assumed that this phenomenon was on a "vagospasm basis," since the pylorospasm disappeared when the vagus fibers to the pylorus were cut without disturbing those to the stomach.

Whether changes of tonus in the pylorus are associated with comparable changes in the body and in the fundus of the stomach is still unsettled. Alvarez³⁸ found that a gradient of muscular rhythmicity may exist which is most marked proximally and which decreases distally

32. Cannon, W. B., and Lieb, C. W.: The Receptive Relaxation of the Stomach, *Am. J. Physiol.* **29**:267, 1911.

33. Daniélopou, D.: Action de l'excitation mécanique du vague au cou sur la motilité de l'estomac chez l'homme, *Arch. internat. de physiol.* **23**:205, 1924. Daniélopou, D.; Simici, D., and Dimitriu, C.: Recherches sur la motilité de l'estomac. Action du vague sur la motilité de l'estomac chez l'homme, *Compt. rend. Soc. de biol.* **91**:493, 1924.

34. Laughton, N. B.: The Effect on the Stomach of Stimulation of the Dorsal Vagus Nuclei, *Am. J. Physiol.* **89**:18, 1929.

35. Veach, H. O.: Studies on the Innervation of Smooth Muscle: I. The Vagus Effects on the Lower End of the Esophagus, Cardia and Stomach of the Cat, and the Stomach and Lung of the Turtle in Relation to Wedensky Inhibition, *Am. J. Physiol.* **71**:229, 1925.

36. McSwiney, B. A., and Wadge, W. J.: Effects of Variations in Intensity and Frequency on the Contractions of the Stomach Obtained by Stimulation of the Vagus Nerve, *J. Physiol.* **65**:350, 1928.

37. Van Liere, E. J.; Crisler, G., and Wiles, I. A.: The Effect of Anoxemia on the Pyloric Sphincter, *Am. J. Physiol.* **111**:330 (March) 1935. Crisler, George; Van Liere, E. J., and Wiles, I. A.: The Mechanism of the Delay in Gastric Emptying Time Caused by Anoxemia, *Am. J. Digest. Dis. & Nutrition* **2**:221, 1935.

38. Alvarez, W. C.: The Mechanics of the Digestive Tract, New York, Paul B. Hoeber, Inc., 1922.

toward the pylorus. However, Brown and McSwiney,³⁹ working on isolated muscular strips, were unable to confirm this. McCrea's observations¹³ showed that the vagus nerves regulate both tonus and movements and that these may be independent of one another. Courtade and Guyon²¹ and Carlson, Boyd and Pearcey²⁵ also noted that the effects obtained on stimulation depend on the existing condition or tonus.

The results reported in the literature regarding the effect of stimulation of the vagus nerve on the pyloric sphincter are conflicting. Langley¹⁹ demonstrated that the body of the stomach and the pylorus received inhibitory as well as motor fibers from the vagus nerve. This was confirmed by May.^{16c} Carlson and Litt¹⁰ reported contracture of the pylorus when there was low or moderate tonus and occasionally relaxation in the hypertonic or spastic stomach. Van Izeren⁴¹ obtained contracture. One of us⁴² observed pylorospasm after stimulation of the peripheral stump of the cut cervical vagus nerve. The evidence indicated that the vagus and splanchnic nerves carry both motor and inhibitory impulses to the stomach as a whole as well as to the pyloric sphincter and that the subsequent result of stimulation is governed by the tonus or peripheral mechanism at the time of the stimulation.

Thomas and Wheelon⁴³ found that stimulation of the vagus nerve produced an increase in the tonus and an increase in the force and frequency of the rhythmic contraction of the pyloric sphincter. They finally concluded that the pyloric sphincter received a double nerve supply consisting of motor and inhibitory nerves by way of the vagus and splanchnic nerves; these nerves, however, are mainly motor in function. Inhibitory fibers may be found in these nerves but more are found in the splanchnic nerves than in the vagus nerve.

Atropine in large doses produced considerable symptomatic relief in this patient. Associated with the clinical improvement, the kymographic records revealed a decrease in the duration of the period of gastric motility with a slight increase in the period of gastric quiescence. The number and amplitude of the contractions were slightly decreased. There was a slight increase in the interval between contractions. An analysis of the results obtained by other investigators revealed that these findings have a sound physiologic basis.

39. Brown, G. L., and McSwiney, B. A.: The Movements and Reaction to Drugs of Strips of the Gastric Musculature of the Cat and Dog, *Quart. J. Exper. Physiol.* **16**:9, 1926.

40. Carlson, A. J., and Litt, S.: Studies on the Visceral Nervous System: On the Reflex Control of the Pylorus, *Arch. Int. Med.* **33**:281 (March) 1924.

41. Van Izeren: *Ztschr. f. klin. Med.* **43**:181, 1901; cited by McSwiney.⁴⁹

42. Barron, Louis E.: Unpublished studies.

43. Thomas, T. E., and Wheelon, H.: The Nervous Control of the Pyloric Sphincter, *J. Lab. & Clin. Med.* **7**:375, 1922.

Smith,⁴⁴ working on the surviving strips of the stomach of various animals, demonstrated that pilocarpine caused contractions of all parts of the stomach which were inhibited by atropine. Tezner and Turolt⁴⁵ confirmed the inhibitory effect of atropine on the human stomach. Brown and McSwiney,³⁹ working on muscle strips, found that pilocarpine stimulated the motor action of the vagus nerve. Atropine produced inhibition. It is the opinion of Carlson, Boyd and Percy,²⁵ Batelli^{16b} and McCrea and MacDonald⁴⁶ that atropine paralyzes the gastric musculature, eliminating control by both the vagus and the splanchnic nerves.

There is sufficient evidence to show¹³ that bilateral vagotomy should not be done in the neck, since esophageal and laryngeal paralysis ensue with subsequent death from infection of the respiratory tract. Intra-thoracic or abdominal vagotomy can be accomplished with a relative degree of safety.

Certain investigators⁴⁷ have reported that either the right or the left vagus nerve may innervate the entire stomach. Bechterew and Mislawski,^{16a} Batelli^{16b} and May^{16c} have noted that stimulation of the left vagus nerve may cause a greater effect than stimulation of the right. Laughton²⁴ also found that faradic stimulation of the cephalic half of the left dorsal vagus nucleus resulted in a more marked effect on the stomach than stimulation of the corresponding part of the right dorsal vagus nucleus. McCrea and his associates⁴⁸ and McSwiney⁴⁹ reported that unilateral vagotomy was without effect.

Our results were striking after anterior (left) abdominal vagotomy. We observed a definite decrease in the duration of the period of gastric motility associated with an increase in the duration of the period of gastric quiescence. One of the outstanding results was the marked increase in the interval between contractions. In one instance it was as much as twelve minutes. The number and amplitude of the contractions were decreased. The resulting hypotonus was striking.

44. Smith, M. I.: The Action of the Autonomic Drugs on the Surviving Stomach, *Am. J. Physiol.* **46**:232, 1918.

45. Tezner, O., and Turolt, M.: Studien über die Wirkung der Verschiebung der K- und Ca- Ionen auf den überlebenden menschlichen Magen, *Ztschr. f. d. ges. exper. Med.* **24**:1, 1921.

46. McCrea, E. D., and MacDonald, A. E.: The Action of Drugs upon the Movements of the Stomach, *Quart. J. Exper. Physiol.* **19**:161, 1928.

47. Succeschi, U.: Sui nervi dello stomaco, contributo alla conoscenza della innervazione viscerale, *Arch. di fisiol.* **2**:521, 1905. Morat, J. P.: Sur quelques particularités de l'innervation motrice de l'estomac et de l'intestin, *Arch. de physiol.* **5**:142, 1893. McCrea.^{15a}

48. McCrea.¹³ McCrea, McSwiney and Stopford.¹⁷

49. McSwiney, B. A.: Innervation of the Stomach, *Physiol. Rev.* **11**:478, 1931.

Carlson⁵⁰ maintained that section of the vagus nerve left the stomach on the whole hypotonic for at least three months. Observations on our patient five months after vagotomy revealed persistent hypotonus at this time. However, Cannon⁵¹ reported that section of the vagus nerve resulted in only temporary loss of gastric tonus and a slowing or weakening of the peristalsis. It would appear that this loss of tone is the result of the subsequent inhibitory action of the splanchnic nerves. We concur with the findings of McCrea and his associates⁵² that experimentation immediately after vagotomy yields unreliable results because of anesthesia and shock. We feel that it is necessary to permit at least a week for convalescence before the effect of vagotomy can be accurately evaluated.

An abnormal retention of gastric contents was observed in our patient during the untreated vagotonic state. With a test meal consisting of 3 ounces of Cream of Wheat, 2 ounces of barium sulfate and sufficient water to form a paste, the total preoperative emptying time in one instance was as much as eight hours. The average emptying time during the control period was six hours and forty-nine minutes. A test meal of moderately thick consistency was intentionally selected in order to avoid some of the discrepancies reported by Meek and Herrin.⁵³ It would seem at this time that the probable cause for this abnormal gastric retention was the pylorospasm obstructing the outlet of the stomach.

Under the influence of large doses of atropine, there was a slight decrease in the emptying time of the stomach. The average time was five hours and twelve minutes, making an average difference of one hour and thirty-seven minutes. The pylorus appeared to be less spastic under this medication. Associated with this there was mild symptomatic improvement.

Striking results followed left abdominal vagotomy. The average total emptying time was reduced to two hours and fifty minutes, an average difference of approximately four hours. During this period particles of barium could be seen passing through a relaxed pylorus, an observation which was not noted during the control period. Our results concur with those of McCrea and MacDonald⁴⁸ in that this reduction in the emptying time is probably the result of a patulous pylorus. Observations made five months after vagotomy revealed an

50. Carlson, A. J.: *Hunger in Health and Disease*, Chicago, University of Chicago Press, 1916.

51. Cannon, W. B.: *Mechanical Factors of Digestion*, New York, Longmans, Green & Co., 1911.

52. McCrea.¹³ McCrea, McSwiney and Stopford.¹⁷ McCrea and MacDonald.⁴⁶

53. Meek, W. J., and Herrin, R. C.: The Effect of Vagotomy on the Emptying Time, *Am. J. Physiol.* **109**:221, 1934.

emptying time of two hours, a difference of four hours and forty-nine minutes. Associated with this marked decrease in the total emptying time, there was definite symptomatic improvement.

Meek and Herrin⁵³ emphasized the fact that the consistency of the test meal was responsible for certain discrepancies reported in the literature. They stated that the evidence pointed to the vagus nerve as being necessary for the existence of gastric tonus and that the emptying depended on the degree of this tonus. They finally concluded that gastric tonus depended on the innervation of the vagus nerve and that vagotomized animals have almost entirely lost gastric tonus. They assumed that the initial decreased emptying time was due to the loss of tonus and the subsequent gravitation of fluids through the pylorus.

McCrea, McSwiney and Stopford¹⁷ observed that after unilateral vagotomy there were paresis and dilatation of the stomach with delay of all motor functions, which they attributed to shock. This persisted for about six days. Paresis then disappeared, and normal function was restored. Observations were made up to twenty-two months, but no change was noticed in the condition of the stomach. After bilateral vagotomy there was a marked decrease in the initial emptying time as well as some decrease in the total emptying time. The early initial emptying of the stomach was the most prominent permanent feature of vagotomy. The authors attributed this to a semipatulous condition of the pyloric sphincter. A decrease in the total emptying time was observed in about 50 per cent of their animals.

Hughson⁵⁴ did not observe acute dilatation of the stomach after section of the vagus nerve. He concluded that section of this nerve in dogs, either at the cardia or on the anterior and posterior walls of the stomach, caused a decrease in the normal emptying time of the stomach.

Opposite results were obtained by Latarjet and Wertheimer.⁵⁵ They found that total resection of the branches of the vagus nerve produced dilatation and atony of the stomach and that these effects were permanent. The contractions seen by them roentgenographically were weak and widely spaced. They noticed a marked delay in the emptying time of the stomach and reported that section of any branch of the vagus nerve resulted in atony of the wall of the stomach with vasodilatation of the vessels in the portion supplied by the sectioned branch. Stimula-

54. Hughson, Walter: The Effect of Vagus Neurotomy on the Pyloric Sphincter, *J. A. M. A.* **88**:1072 (April 2) 1927; Reflex Spasm of the Pylorus and Its Relation to Diseases of the Digestive Organs, *Arch. Surg.* **11**:136 (July) 1925.

55. Latarjet, Cluzet and Wertheimer: Effets de la section et de l'excitation des nerfs propres de l'estomac sur la motricité de cet organe, *Compt. rend. Soc. de biol.* **84**:985. 1921.

tion of any of the branches produced hypermotility in the part supplied by the branch. After total section, they observed a relaxed pylorus.

Many deleterious effects have been reported after vagotomy. Our studies have not substantiated any of these reports. Alvarez,⁵⁶ from his work on rabbits, reported a mortality of 49 per cent after vagotomy. In many animals death was due to diarrhea and inanition. Auer⁵⁷ reported the occurrence of ulcer in a number of his vagotomized rabbits. However, this relationship is rarely observed in the stomach of man or of the cat or dog. Donati⁵⁷ obtained negative results in dogs. Greggio⁵⁸ found ulcers in only a small percentage of his dogs. Durante⁵⁹ reported that lesions of the gastroduodenal nerves, that is, the vagus and the sympathetic nerves, may produce ulcers. Koennecke²⁴ observed hemorrhagic and thrombotic processes throughout the gastro-intestinal tract in a dog subsequent to bilateral subdiaphragmatic vagotomy. Ivy⁶⁰ found that dogs dying immediately after section of the vagus and the splanchnic nerves not infrequently show petechial hemorrhages of the pyloric and duodenal mucosa. However, there were several dogs with no gastric or duodenal lesions after resection of the vagus and splanchnic nerves. Most of Ivy's animals lived indefinitely, and section of the nerve was verified at necropsy. Repeated clinical and roentgenographic examinations of our patient failed to reveal any evidence of gastroduodenal ulcers throughout any period of the investigation. There was marked subsequent clinical improvement with the complete disappearance of gastro-intestinal distress after vagotomy.

CONCLUSIONS

Hypermotility and hypertonicity of the stomach were observed in a patient manifesting the symptom complex of vagotonia as described by Eppinger and Hess.³ Associated with these findings there appeared to be pylorospasm. The hypermotility and hypertonicity were associated gastrographically and fluoroscopically with epigastric distress.

56. Alvarez, W. C.: The Effect of Degenerative Section of the Vagus and Splanchnic Nerves on the Digestive Tract, *Proc. Staff Meet., Mayo Clin.* **4**: 205, 1929; The Effect of Degenerative Section of the Vagus and Splanchnic Nerves on the Digestive Tract, *Am. J. Physiol.* **90**:631, 1929.

57. Donati, M.: Experimentelle Versuche das Magengeschwür vermittels Verletzungen der Magennerven hervorzurufen, *Zentralbl. f. Chir.* **31**:346, 1904; *Arch. f. klin. Chir.* **73**:908, 1904.

58. Greggio, E.: Des ulcères gastro-duodénaux, *Arch. de méd. exper. et d'anat. path.* **28**:533, 1917.

59. Durante, L.: The Trophic Element in the Origin of Gastric Ulcer, *Surg., Gynec. & Obst.* **22**:399, 1916.

60. Ivy, A. C.: Contributions to the Physiology of the Stomach: LII. Studies on Gastric Ulcer, *Arch. Int. Med.* **25**:6 (Jan.) 1920.

During intense medication with atropine there was a slight decrease in the duration of periods of motility. This was associated with a slight increase in the duration of the periods of quiescence. A slight decrease in the number and amplitude of the contractions associated with a slight increase in the interval between contractions was also noted. This slight decrease in gastric tonus was associated with mild symptomatic relief.

After anterior (left) abdominal vagotomy there ensued a marked decrease in the duration of periods of motility associated with a marked increase in the duration of periods of gastric quiescence. The number and amplitude of the contractions were noticeably diminished. The interval between contractions was markedly increased.

An analysis of studies of the gastric motility made five months after vagotomy revealed that the decrease in the duration of periods of motility and the decrease in the tonicity of the stomach were still evident.

During the untreated stage the emptying time of the stomach was delayed. This we would attribute to pylorospasm.

During medication with atropine the stomach emptied its contents one hour and thirty-seven minutes sooner than during the control period.

After left abdominal vagotomy the stomach evacuated its contents four hours sooner than during the control period.

Five months after vagotomy this decrease in the emptying time still persisted.

There was no evidence at any time of acute dilatation of the stomach.

The results of vagotomy were attended by definite symptomatic improvement. At no time could we obtain clinical or roentgenographic evidence of subsequent lesions of the gastro-intestinal tract.

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SCOLIOSIS

A FUNCTIONAL DECOMPENSATION

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Scoliosis may be defined as an abnormal, persistent lateral curvature of the spine with symptoms due to functional decompensation of the back.

The history of scoliosis dates back to the most ancient known civilization. The presence of the lateral curvature of the spine was familiar to the ancient Egyptians. Hippocrates left a description of scoliosis and even suggested a remedy. However, the actual understanding of scoliosis has remained obscure. One of the important steps in the development of present day knowledge occurred at the time of Hessel. Hessel was a mechanical genius who made a form-fitting brace which gave sufficient support to the back so that a patient with scoliosis who wore one of these braces received definite benefit. This was the beginning of the supportive treatment for scoliosis. The opposing school developed under Ling in Stockholm. Ling had the conception of making a perfect body by developmental exercises. The use of the various types of exercises and corrective strengthening received its great impulse from the fact that marked improvement was noted as a result of gymnastic therapy. Later, orthopedic surgeons developed the combination of supportive and corrective treatment. In addition, they have added much to the understanding of the condition both as to its development and as to its etiology.

Before going on to a discussion of the pathologic process of scoliosis, it is essential to define some of the common terms used in describing the condition. The terms primary curve and secondary curve are frequently used; the primary curve is the original curve, and the secondary curve is the compensatory curve. Anatomically, one speaks of a right or left curve, depending on the direction of the deviation. The term "structural scoliosis" is sometimes used to describe the presence of abnormalities in the bones and ligaments. If the curve is a single simple curve, it is spoken of as a C curve; if there is a compensatory curve present, it is called an S curve. Usually the lateral curvature is associated with torsion of the vertebral column; this is termed rotation. The location in which the curvature occurs is used further to define the scoliosis; for instance, one speaks of right lumbar or left lumbar scoliosis. The changes in the bone and in the soft tissues tend to limit the motion of the spine and to bring about what is clinically known as fixation; it limits one of the functions of the back, that of motion, but aids the more important function of maintaining the erect posture of the body. When

the back is capable of carrying out this function, it is said to be sufficient; an insufficiency arises when there is weakness in the structures of the back or when the normal back is overstrained by too great a load.

MORBID ANATOMY

The structural changes that occur make up the actual morbid anatomy. The primary structural changes are those which give rise to scoliosis; the secondary structural changes result from the altered statics brought about by the curvature. The bony changes that occur as primary structural changes are congenital malformations of the vertebrae and the destruction of the vertebrae by disease such as tuberculosis, osteomyelitis or tumor. Secondary bony structural changes consist in the altered shapes of the vertebrae. The vertebrae are wedge shaped, with the narrow margin toward the concavity. The articular facets are broader and more horizontally placed than normal. The intervertebral foramina are narrowed; the transverse process on the concave side is narrower than normal, and the vertebral foramen is egg shaped instead of round. The presence of strain and irritation frequently causes overgrowth or exostoses at the vertebral margins; at times these are extensive enough to cause a certain degree of fixation. With the presence of strain there is loss of joint space, particularly at the convex side, between the vertebrae. The intervertebral disks are compressed and become wedge shaped. A certain amount of fibrous change occurs in the disks; the joint surfaces become irregular, and there is loss of cartilage until actual fusion occurs. The ligaments accommodate themselves to the altered position of the spine and are stretched on the convex side and short and thick on the concave side of the curvature.

The changes in the muscles vary with the different types of scoliosis, as, for instance, the muscular changes seen in scoliosis caused by spastic hemiplegia and those associated with scoliosis caused by infantile paralysis. In the latter there is an actual flaccid paralysis which may involve any one group or even individual muscles of the back or abdomen, while in the former there are hypertonic muscles on one side. In the adolescent type of scoliosis the muscles on the convex side are thin and stretched and show fibrous changes while the muscles on the concave side are shortened and may show fatty degeneration. Other anatomic changes that occur concomitant with the lateral curvature are an increased posterior curve in the dorsal area (rounded kyphosis) and an increased anterior curve in the lumbar region (lordosis). Rotation is frequently present, and the effect on the chest is marked. The ribs, which act as long levers attached to the vertebral column, show a marked deformity; the result is compression of the wall of the chest on one side. Frequently this distortion is so marked as to interfere with the normal use of the lung, and at times it compresses the heart or even the aorta and vena cava.

In order to understand the development of the curvature which makes up the scoliosis, a few normal anatomic and physiologic facts should be emphasized. Significant is the fact that there are normally present four anteroposterior curves.¹ The primary curves are a posterior curve in the dorsal area and a posterior curve in the sacral area. The anterior curves in the lumbar and cervical areas develop after the child assumes an upright position, and these are therefore considered compensatory or secondary curves. One lateral curve is normally present in the dorsal area; this is usually to the right, although it may be to the left, the variations being dependent on race, occupation and other factors.

Of physiologic importance is the fact that the primary function of the back is to hold the upright position;² furthermore, the human body will always attempt to assume the upright position. Movement in the dorsal area is relatively limited, 80 per cent of the motion of the spine being in the lumbar area. In addition, one must remember that structures will grow, within limits, according to the demand made on them. It is not difficult to understand the development of a lateral curvature secondary to a tilt in the pelvis; the lateral curvature is compensatory in order for the body to retain the upright position. Similarly, there is a compensatory dorsal lateral curvature in the presence of torticollis. Relatively easy to understand, also, is the lateral curvature of the spine caused by the contracture of the pleural cavity. That spastic paralysis of one side would cause some degree of lateral curvature is to be expected. The imbalance in weight bearing caused by a laterally wedge-shaped vertebra, whether due to a congenital anomaly or to destruction by disease, gives rise to scoliosis. The explanation of the curvature in anterior poliomyelitis is more involved. It is readily seen that a curvature will develop when the muscles on only one side of the back are paralyzed; however, there are scoliotic curves which develop when paralysis in the muscles is relatively symmetrical. The development of the curves in these cases may be explained on the same basis as those in the so-called adolescent type of scoliosis.

Rachitic scoliosis is due to a softening of the structures, particularly the bony structures in the vertebrae; hence, when normal stress is applied there is a tendency for an increase of the normal lateral curvature with the development of compensatory curves. The severity of the curvature is dependent on the degree of weakness caused by the rickets as well as on the amount of stress applied.

Adolescent scoliosis is so called from the period at which it most frequently occurs, but like rachitic scoliosis, it is due to a weakness in

1. Morris, H.: *Human Anatomy*, edited by C. M. Jackson, ed. 9, Philadelphia, P. Blakiston's Son & Co., 1933, p. 103.

2. Magnus, Rudolf: *Some Results of the Studies in the Physiology of Posture*, *Lancet* 2:531-536 (Sept 11); 585-588 (Sept. 18) 1926.

structure. The primary weakness is in the muscles,³ although the ligaments and bones show some loss of strength. If there is an imbalance between the capacity of the back to do its normal work and the demand made on the back there will ultimately be an increase in all the normal curves; therefore, the first physical sign is usually an increase of the anteroposterior curves, which is recognized as poor posture. If the imbalance continues, the lateral curvature will also increase and scoliosis will develop; ultimately there will be compensatory curves to the dorsal curve in the lumbar and cervical areas. Therefore, scoliosis develops whenever there is a decrease in strength of the structures of the back (loss of capacity) or if there is an increase in the demand made on the back (overload), or a combination of the two. In the presence of such a condition, decompensation develops; the word insufficiency is sometimes used for decompensation. The decompensation refers to an imbalance in the function and gives rise to symptoms of fatigue and strain. A prolonged period of decompensation will result in an increase in all the normal curves, which means a lateral curvature; this condition is called scoliosis. With the occurrence of lateral and anteroposterior curvatures, the effect on the vertebral column must be torsion or rotation. The greater the decompensation and the more prolonged the duration of the scoliosis, the more severe the curvature will be and the more marked the actual structural changes.

ETIOLOGY

The various clinical forms of scoliosis are best classified on the basis of etiology. There are, first of all, two distinct types—congenital and acquired.

The congenital scolioses are of one of two types. 1. The first type is due to an anomaly. There is a definite deformity which can be demonstrated roentgenographically; the lateral side of one or of several vertebrae is only partially formed, or one or more vertebrae may be absent, resulting in a relatively sharp lateral curvature in the direction opposite the involved side. In cases of severe involvement there will be a compensatory curve above and below this primary curvature. In many instances, however, the structure, even though badly formed, will be highly efficient, and there will be no decompensation. In such cases the deformity is the only abnormality, and the prognosis for any change in the deformity is practically nil; on the other hand, no symptoms in the way of impaired function will develop. 2. The second type of congenital scoliosis is probably due to the prolonged retention of the lateral posture in utero; in this type there is the simple C curve. The roentgenographic picture is normal; the curvature, however, tends to persist, particularly when the body assumes the upright position; the spine is

3. Hauser, Emil: The Muscle Factor in Adolescent Scoliosis, *J. A. M. A.* 98:1535-1538 (April 30) 1932.

pliable. With corrective measures the prognosis for full recovery, both anatomically and functionally, is excellent.

Acquired scolioses may be divided as into the following types.

Curvature Due to Rickets of Osteomalacia.—The existence of fetal rickets and its relationship to scoliosis is still problematic. The occurrence of static deformities and the presence of rickets are well known. Owing to softness and weakness in the structures of the back, there is an increase of all the normal curves; so there may be rachitic kyphosis as well as the rachitic scoliosis. The roentgenogram shows changes in the bone. The presence of the other signs of rickets helps to establish the diagnosis. Usually rachitic scoliosis is severe. The prognosis is dependent on the early recognition of the condition. If a highly developed curve has been allowed to persist until the child has reached adolescence, little can be done in the way of correction of the deformity. The prognosis as to function, however, is relatively good.

Scoliosis due to osteomalacia may be explained in the same manner. The condition, fortunately, is rare; the prognosis is poor.

Scoliosis Due to Flaccid Paralysis (Anterior Poliomyelitis).—Scoliosis due to infantile paralysis presents the most bizarre forms. This is to be expected in view of the various muscles affected, as well as the varying degrees of paralysis present in each muscle. A marked asymmetrical paralysis will definitely affect the degree of the curvature. The most severe types of scoliosis seen occur as the result of infantile paralysis; one sees not only the highest degree of deformity but, owing to the paralysis, marked incapacity. In connection with poliomyelitis, it has been observed that paralysis of the abdominal muscles will give rise to a scoliotic curvature. The explanation offered is that it is impossible for the muscles of the back to act as the function of the abdominal muscles, which act as opponents, is completely lost. The inability of the muscles to act results in a loss of normal function of the back, namely, to hold the erect position; the result is an increase of the curvatures, including the lateral curvature, and, therefore, scoliosis. The prognosis in these cases is dependent on the amount of recovery possible in the nerves and, ultimately, in the muscles. The early paralysis, owing to edema, will, if properly cared for, permit recovery in strength. The prognosis, therefore, depends on adequate treatment in the early stages and on the development of power in the remaining muscles. If the paralysis is so severe that even with proper treatment there is insufficient strength to hold the upright position, scoliosis will inevitably result. The severity of the scoliosis and the amount of disability can be controlled, to some extent, by supportive measures. In this connection it is important to realize that there is a natural tendency in the body to create a fixation which will increase the stability as well as the capacity of the back. The curvature ultimately reaches a point where it becomes fixed and acquires a certain degree of compensation so far as function is con-

cerned, so that with limited functional demands the patient may be relatively free from symptoms in spite of a deformity. Of course, with the severe deformities there are decrease of vital capacity and impairment of cardiac function, which means a shortening of life expectancy.

Scoliosis Associated with Syringomyelia.—It is estimated that 80 per cent of all persons with syringomyelia have an associated scoliosis; in fact, it is one of the first symptoms to appear. The curvature is usually higher than in other types of scoliosis; characteristic also is the fact that it is slow in acquiring fixation; in other words, it remains mobile for a long time. The severity of the condition varies. In late stages kyphosis and deformity of the chest develop. The cause of the scoliosis is not certain. It is believed that it is due to trophic disturbances in the bone. The pathologic process is a spastic paralysis with dissociation of sensation—retention of touch and loss of heat and pain senses. Among the trophic changes are swelling in the hands, thickening of the skin and arthropathies. The lesion is in the spinal canal and may be a gliosis, a tubelike cavity or a degenerative change in other parts of the cord due to pressure. The primary condition is usually progressive, which, of course, determines the prognosis.

Curvature Due to Spastic Palsy (Hemiplegia).—When spastic paralysis involves one side of the body, a lateral curvature develops in an effort to establish a balance; this is, to a certain extent, a compensatory curvature. The prognosis is dependent on the possibility of clearing up the spastic paralysis. This type of scoliosis does not give rise to a functional disturbance.

Scoliosis Secondary to Deformities Elsewhere in the Body (Static Deformity).—Any deformity that causes a pelvic tilt, such as an anomaly in the development of the pelvis or shortening of one limb as a result of anterior poliomyelitis, tuberculosis, fracture, epiphysial slipping, contractures of the hip and knee, dislocations of the hip or unilateral genu valgum, will give rise to a lateral curvature in the lumbar area; compensatory curves may develop, giving rise to an S-shaped scoliosis. The curve develops in compensation for the malposition of the pelvis and is the result of correction, to enable the body to hold the erect position. The prognosis is dependent on the possibility of correcting the pelvic tilt. The condition usually is not progressive.

Scoliosis Due to Torticollis.—The presence of torticollis, whether congenital or acquired, gives rise to a secondary compensatory curve in the dorsal area. A one-sided cervical rib would have the same effect. This type of scoliosis may also develop secondary to a congenital elevation of the shoulder. The prognosis in these cases is dependent on the possibility of correcting the primary deformity.

Curvature Due to Local Disease of the Spine.—Any lesion that destroys the lateral part of one or of several vertebrae will result in an

angular type of scoliosis in that area; secondary curvatures will develop later. Tuberculosis occasionally causes such a destruction. At times one sees the same type of scoliosis as a result of a malignant condition. Rarely, a fracture of the vertebral body will give rise to a lateral curvature. The scoliosis in such cases is of relatively minor importance in comparison with the primary disease.

Curvature Secondary to Contracture of the Chest.—A contracture in the wall of the chest, whether due to pleurisy or thoracoplasty, will result in a lateral curvature in the dorsal area. Rotation occurs early in this type of scoliosis. The ribs exert an influence on the spine so as to cause rotation and lateral curvature. The prognosis is good so far as the arrest of the progress of the deformity is concerned.

Lateral Curvature Due to Sacro-Iliac Disease or Sciatica.—In reality such a curvature is a protective list and not true scoliosis. The curvature or list will subside if the pain is relieved.

Hysterical Scoliosis.—This type of scoliosis occasionally occurs in women and, in rare instances, was seen in men during the World War. Usually other signs of nervous irritability are present. Of diagnostic value is the fact that the scoliosis disappears under anesthesia.

Adolescent Scoliosis.—This type of scoliosis has also been called idiopathic, static, occupational, habitual, postural or simple scoliosis. The term "idiopathic" should be eliminated as obsolete, as the etiology no longer remains unknown. The scoliosis develops secondary to a functional insufficiency of the back. Anything that decreases the normal capacity of the back or increases the load beyond normal, or a combination of these factors, will tend to give rise to an adolescent scoliosis. One of the principal factors that decrease the normal strength of the back is the rapid growth that occurs during the period of adolescence. Debilitating diseases lower the strength of the back, which accounts for the scoliosis which occurs after scarlet fever. In children physically below par, if they are not guarded, scoliosis slowly develops. This failure of sufficient structural development may be due to the lack of proper food. Insufficient air and sunshine will act as additional factors; inadequate physical exercise is an important factor. The introverted child with studious tendencies and poor muscular coordination is prone to lateral curvatures of the spine. The load may be increased unilaterally by the carrying of heavy books on one arm. Most important, however, is the abuse of the primary function of the back, namely, the holding of the erect position of the body. If this function is unduly prolonged, a strain will result. Formerly this was a frequent occurrence among school children. At times the load may be increased by excessive body weight. Usually it is a combination of several of these factors over a relatively prolonged period of time that accounts for the development of scoliosis during adolescence. It is possible that rickets may also play a rôle,

particularly the so-called "late rickets." Unrecognized congenital malformations, particularly in the fifth vertebra, may play a more important part than is realized in the development of scoliosis during adolescence. In this country adolescent scoliosis occurs more frequently than all the other types combined. This is not true in European countries where scoliosis due to rickets occurs more frequently than the other types. It is difficult to say just when the adolescent scoliosis develops. Children usually are brought in for attention during the school age; the average age seems to be about 13 years. It is evident that the curvature arises some time previous to the time of examination.

With regard to symptoms, in the incipient stage adolescent scoliosis is a simple C curve in the dorsal area. Right dorsal and left lumbar curves occur in about 80 per cent of the cases; in the other 20 per cent the curves are inverted, that is, left dorsal and right lumbar curves. Rotation appears by the time the posterior curves develop. In the dorsal area the ribs emphasize the rotation, and the deformity of the chest is marked, while in the lumbar region the transverse processes are comparatively short, and the rotation, although equally great, is not apparent. In the usual form of scoliosis the left shoulder drops lower than the right; the right scapula projects posteriorly and is high; the left wall of the chest is compressed posteriorly, with the ribs curved downward. The vital capacity is diminished; the shoulders droop forward, and the normal lumbar curve is accentuated. The torso seems to be shortened, and the body tends to list toward the affected side. The patient usually complains of fatigue and backache. These are the chief symptoms of muscular insufficiency of the back. In cases of extreme involvement the nerve is impinged, causing severe pain along its distribution. There is inability to carry out normal exercises. Frequently there is an associated awkwardness; many of the children are extremely sensitive and shy and have an inferiority complex.

The curvature usually grows progressively worse if left untreated, provided the causative factors continue to exist. In many instances the causative factors are removed without actual recognition of their importance. Complete recovery may result. Even when a curvature has developed, the condition in some cases is arrested simply by means of participation in athletic sports; on the other hand, strenuous athletics may increase the deformity.

The principal complications have already been indicated under symptoms—cardiac decompensation, decrease of vital capacity and altered psychology.

The prognosis in cases in which treatment has been given is variable, depending on the extent and severity of the scoliosis. In extreme scoliosis of long standing it is impossible to obtain complete correction of the deformity; in the early stages satisfactory correction and retention of normal position can be accomplished. The best prognosis is held

in those cases in which the first signs of the lateral curvature are recognized and prophylactic treatment is immediately instituted. In the cases of severe involvement, even though the deformity cannot be corrected, the functional capacity can be greatly increased.

TREATMENT

The object of treatment in scoliosis is twofold: the reestablishment of normal function and the correction of the deformity.

In reviewing the methods of treatment, only those which offer some definite principle are included. With the introduction of the form-fitting corset by Hessing, supportive treatment was first used to give relief from the strain and to bring about some correction. These corsets were of several types. They were applied with the body extended, with reinforcements beneath the convexity; counterpressure was applied to the sacrum. The principle involved in the Hessing corset is used in modern treatment.

The principle of exercise in various forms has been recommended, for example, passive exercise, in which force is directed against the convexity, and active exercise; the latter has been found the more satisfactory. Various systems have been devised; however, more important than the particular system used is the fact that the exercises are graduated to the needs of the patient. Exercises to increase the strength of the muscles only on the side of the convexity were used for many years. Some even went so far as to attempt to reduce the strength on the concave side. It was found that all exercises that increased the strength of the muscles, whether the muscles of the abdomen, back or shoulder or of the pelvic girdle, were beneficial in the treatment of scoliosis. Greater mobility is possible with the body in the horizontal position, and exercises on the hands and knees were prescribed. By the same token, swimming can be considered a beneficial exercise, particularly as an early exercise for weakened muscles. Corrective exercises in which the patient voluntarily stretched the body by means of a Sayre attachment to the head have been used. Many types of apparatus consisting of mechanical levers to increase the force have been invented. Some of these have been combined with mechanisms for extension.

Correction by means of hyperextension frames and by plaster of paris beds, in which the body was held in a corrected position, has been attempted. The disadvantage of prolonged hospitalization and rest in bed is the resultant increase in structural weakness.

Treatment by means of forceful correction, with retention of the corrected position by means of a plaster of paris cast, has been tried. Abbott developed this type of treatment to a high degree. However, the severity of the pain, the development of pressure sores and the inability to increase the strength during treatment ultimately made it necessary to abandon this form of correction.

Derotation is another fundamental principle in the correction of the scoliotic deformity. This has been attempted by means of elastic straps passing over the shoulder and down around the pelvis and acting as a derotating coil. Another method fixes the chest in a vice; the pelvis is fixed on a seat that can be tilted and rotated; with the upper part of the body fixed, the pelvis can then be turned to bring about a derotation. When the desired position is attained, the chest, the trunk and the pelvis are held with a plaster of paris cast. Correction can be obtained in this manner, but again it is difficult to reestablish the capacity to retain correction. A more simple method to obtain the same result is to fix the pelvis by means of a horizontal bar on an upright frame and to derotate by turning the shoulder girdle, using the arms as levers.

The treatment of scoliosis is dependent on the etiologic factors. In congenital scoliosis the presence of an anomaly does not permit the actual removal of the causative factor. Attempts have been made to remove the hemivertebra in order to balance the spinal column. Surgical removal can actually be carried out, but the improvement obtained does not justify the procedure. Furthermore, it is questionable whether the capacity is not decreased rather than increased. The most important part of treatment is to prevent a further increase of the curvature. This is best accomplished by the use of functional exercise, that is, by treating the child as though it were normal. In other words, the use of braces, unless there is an additional factor, is contraindicated.

Congenital scoliosis due to intra-uterine posture can be corrected even before the child is able to sit up. If the deformity tends to persist, it may be advisable to use a plaster of paris bed with the curvature in the opposite direction. The child can sleep in such a bed, and correction is attained. Furthermore, the parents can hold the child in such a way that there is a tendency for the deformity to be corrected. If the curvature is not recognized until the child begins to walk, it is occasionally necessary to apply a plaster of paris jacket, with the child held in the overcorrected position. Once such a jacket is applied, it is important to make certain that exercises are carried out to keep up the general strength of the body. The more rapidly this correction can be attained and all supportive treatment discontinued, the better the result.

In the treatment of scoliosis due to rickets, the problem is twofold. In active rickets the process of deformity is progressive. During this period correction can be attained; this can be done by means of casts and braces. However, of primary importance is the treatment of the rickets itself; this, of course, includes a complete antirachitic regimen. The earlier this is instituted the more satisfactory the result. The scoliotic deformity may progress after the actual rickets has subsided; this deformity is fixed. Only in the preadolescent stage is there hope for improvement so far as correction of the curvature is concerned. Of prime significance, therefore, is the attainment of the maximum amount

of function. When this is accomplished, even though the deformity may persist, the child will be able to lead a normal, useful life.

Scoliosis due to anterior poliomyelitis offers the most difficult phase of the scoliotic problem. The final solution of the problem must be the prevention of infantile paralysis. The early recognition of the involvement of muscles of the abdomen and back in cases of poliomyelitis and the protection of such muscles until they regain the maximum amount of strength are of primary importance. In the reestablishment of strength, exercises are essential; under-water therapy and swimming are important. The back must be protected against the development of a curvature. In this connection, the patient should be permitted to sit or stand for only a brief period; as the strength of the muscles increases, the length of time may be gradually increased. The use of massage and muscle training is essential, as in any case of paralysis. In those cases in which in spite of the best treatment (protection and exercise) there is insufficient strength, a support is necessary. The extent of the paralysis and the weight of the patient determine the type of support to be used. Form-fitting supports are preferable; one may use a jacket of leather and steel or of celluloid, or a corset made of cloth reenforced with stays. With time there is a tendency for fixation of the curvature; this may ultimately be sufficient to permit the patient to discard the support. To hasten the fixation, the fusion operation is of benefit. If the back has not been protected and the curvature is exaggerated, some correction may be taken before the fusion operation is performed; either a Hibbs or an Albee operation may be done, or a graft may be placed in the convexity to act as a supportive column or prop.

The treatment of scoliosis associated with syringomyelia must be directed against the disease itself. Laminectomy with drainage of the cavity fluid has been done, although the use of anesthesia in such cases is dangerous; cervical puncture, exposure of the spinal column to the roentgen rays and the use of mercury and iodides have been tried.

In spastic palsy, treatment of the scoliosis is dependent on the improvement of the hemiplegia and may include correction of the equinus deformity.

In scoliosis due to a deformity elsewhere in the body, for instance a pelvic tilt, correction of the curvature must be directed against the pathologic process which causes the pelvic tilt. If this is a tuberculous hip, the adduction and flexion deformity must be corrected. Frequently a slight raising of the shortened limb will be followed by improvement.

Scoliosis in the dorsal area found in torticollis subsides with correction of the torticollis. If a cast is applied to hold the correction of the head and neck, it may also include an overcorrection of the dorsal area.

For scoliosis due to a destructive lesion of the vertebrae, the treatment is limited to treatment of the lesion itself.

Scoliosis which develops secondary to pleurisy or thoracoplasty cannot be completely corrected, but some improvement is obtained by exercises, particularly deep breathing and the holding of the erect position of the body.

The protective list secondary to sciatica and sacro-iliac disease disappears spontaneously with relief of the primary condition.

The treatment of adolescent scoliosis consists of (1) prophylaxis, (2) correction of the deformity and (3) reestablishment of normal function. Prophylactic treatment necessitates early recognition of an abnormal lateral curvature. Suggestive is the history of fatigue and bad posture in a rapidly growing child. The disrobed child is examined for any increase in the normal curvatures of the vertebral column and the presence of a pelvic tilt. All causative factors are investigated and, whenever possible, eliminated. Strain is relieved by periodic rests; strength is increased by graduated exercises; food deficiencies are replenished by a high caloric diet and, at times, with feeding at intervals. Secondary anemia is treated with iron and liver extract; vitamins are supplied in ample doses, and calcium is added to the diet. The child is encouraged to take part in outdoor activities which include fresh air and sunshine.

If a scoliotic deformity is already present, the curvature must be corrected. The method of correction used is based on the teaching of Professor Haglund.⁴ The pelvis is leveled. The dorsal curve is relatively fixed, while the lumbar curve is freely movable and readily corrected. Therefore, in the presence of a right dorsal curvature, if the trunk of the body is made to list to the left, the left lumbar lateral curve is obliterated. In a similar manner, in the presence of kyphosis in the dorsal area the compensatory lumbar lordosis is obliterated by tilting the body forward. Derotation is obtained by fixing the pelvis and rotating the shoulder girdle in the opposite direction, with the arms acting as levers. In this position, if the pelvis is fixed with a plaster of paris jacket which incloses the lumbar area and extends up to the dorsal curve, correction will follow. The body will assume the upright position due to the body-righting reflex. The result will be a correction above the cast in the region of the right dorsal curvature. This correction is controlled by natural forces.

In addition to correcting the deformity, the cast also acts as a support to relieve the functional decompensation. At the same time it permits normal use of the body structures. The patient can pull himself out of the cast and can go on with practically all normal activities. The treatment is entirely ambulatory, permitting the child to go to school.

In early stages full correction can be obtained by this method. To retain the correction it is necessary to reestablish the normal capacity of

4. Haglund, Patrik: *Die Entstehung und Behandlung der Skoliosen*, Berlin, S. Karger, 1916.

the back. To do this, after the cast has been removed the normal position is held by means of a support, which may be either a steel and leather jacket or a reenforced cloth corset, until the structures have been developed by exercises. The exercises used are graduated physiologic exercises, that is, the carrying out of the normal functions of the back, so that ultimately there is sufficient fixation to give full compensation, which will prevent a recurrence of the deformity.

In cases of severe involvement of long standing, with fixation, it is not possible to obtain complete correction. If the back is compensated, even though the deformity is marked, it is best not to attempt correction, as in breaking down the fixation there is danger of bringing about a decompensation. However, if the patient suffers from pain due to pressure on the nerve, then in spite of the fixation it is necessary to take sufficient correction by the foregoing method to relieve the symptoms.

In order to obtain fixation more rapidly, a fusion operation may be performed. A fusion operation in itself obviously cannot correct the scoliosis. The method most frequently used is the forceful correction by means of turn-buckle casts, followed by a fusion with bone grafts. It has been found that in those cases in which compensation and fixation were obtained after fusion operation, the correction was retained; however, if the decompensation persisted in spite of the bone graft, the deformity continued to increase (Steindler).⁵

The problem of scoliosis is not solved, but with a better understanding of the condition the ultimate outlook for the prevention of a deforming scoliosis is good. This is particularly true of the adolescent type of scoliosis. The answer in the other types of scoliosis lies in the prevention of the disease causing the curvature.

SUMMARY

A new conception of scoliosis is presented. Scoliosis is due, not to an imbalance in the pull of the muscles of the back, as is commonly believed, but to an increase of the normal curvatures of the back. This increase of the normal right dorsal lateral curvature is brought about by a decompensation in the functional capacity of the back. The development of the structural changes is explained. The etiology of adolescent scoliosis is given for the first time and utilized to prescribe prophylactic measures. In addition, a new type of corrective treatment is described. Not only is the deformity improved, but all the secondary disturbances in function are relieved. This method of treatment has been applied successfully over a period of ten years. Owing to the prevalent confusion as to the conception of scoliosis, it was necessary to treat the general consideration of the subject with thoroughness.

5. Steindler, A.: The Compensation Treatment of Scoliosis, *J. Bone & Joint Surg.* 11:820-830 (Oct.) 1929.

EFFECT OF CINCHOPHEN ON THE GASTRIC SECRETION

AN EXPERIMENTAL STUDY

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The administration of cinchophen is an effective method for the production of chronic peptic ulcer in dogs. The ulcer thus produced is similar in most respects to the lesion seen in human beings. The ulcer begins as a diffuse gastritis with destruction of the mucosal cells and the formation of multiple erosions throughout the gastric mucosa. These erosions become acute ulcers, which tend to heal. The majority do heal, but one persists as a chronic ulcer, and the gastritis subsides. This chronic lesion is usually situated from 2 to 3 cm. from the pyloric ring on the lesser curvature or on the posterior wall of the stomach. Occasionally, two or more gastric ulcers are present, and there may be an associated duodenal ulcer in a small percentage of the animals. The ulcer readily heals when the administration of cinchophen is stopped.

Many controversial articles have been written on gastric secretion. In general, it is thought that the presence of some free acid in the stomach is necessary for the development of a peptic ulcer. There are reports of peptic ulcer, however, in the presence of achlorhydria, although this occurrence has been contradicted. Whether or not hyperacidity develops in the human stomach before the peptic ulcer forms is not known. There is usually hyperacidity in the presence of peptic ulcer, but this finding is not constant. There is no evidence which demonstrates that a peptic ulcer is more prone to develop in the presence of hyperacidity than it is in the presence of normal acidity. There is hypersecretion in the human stomach during the active stage of peptic ulcer, but it is not known whether this exists prior to the development of the ulcer or not. There are usually hyperacidity and hypersecretion in cases of acute gastritis, and there usually are decreased acidity and hyposecretion in cases of chronic gastritis.

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In view of these findings in the human stomach, we thought that a study of the acidity and the volume of gastric juice secreted during the various phases of development, activity and healing of peptic ulcers which were experimentally produced by the administration of cinchophen would be of interest.

METHODS

Two groups of dogs were used. Both received routine kennel care and were fed a diet composed of cracker crumbs, ground horse meat and evaporated skimmed milk. The food was weighed and fed in sufficient amount to meet the caloric requirements of the animal.

Group 1 consisted of twelve dogs, each of which weighed about 17 Kg. Fractional gastric analysis was performed every second or third day after a fast of twenty-four hours. A large rubber catheter was passed into the stomach, and the residual gastric secretion of the fasting state was removed. One and a half milligrams of histamine phosphate was then given subcutaneously. Each fifteen minutes thereafter the gastric contents were removed. This process was continued until the value for the free acidity returned to the fasting level.

The free and total acidity and the total volume of secretion were determined for each specimen. The free acidity was determined by titrating 2 cc. of filtered gastric contents against a tenth-normal solution of sodium hydroxide, dimethyl-amino-azobenzene being used as an indicator. The total acidity was determined by a similar titration, with phenolphthalein as an indicator. It was found that there was a consistent difference of never less than 7.5 or more than 12.5 cc. of tenth-normal solution of sodium hydroxide per hundred cubic centimeters of gastric juice between the value for the free and that for the total acidity. Both the free and the total acidity were determined in every specimen, but throughout our results we shall consider only the total acidity.

When a series of five or more fractional analyses had been made with consistent results, the administration of cinchophen was begun. Two grams of this drug, well mixed with the diet, was given daily. The gastric analysis was continued throughout the developmental, the active and the healing stages of ulceration. In many instances, when typical symptoms were present, exploratory laparotomy confirmed the presence of an ulcer. After an ulcer had developed the administration of cinchophen was stopped, but the study of the secretion was continued. All dogs were eventually killed, and necropsy was performed.

Group 2 consisted of five dogs, each of which weighed about 12 Kg. Each dog had a fundic pouch. These pouches were made from the greater curvature of the stomach. The splenic vessels attached to the fundus were kept intact, and the pouch was left in the abdominal cavity. The contents, which were collected continuously, drained through a de Pezzer catheter into a balloon carried in a basket on the side of the dog. No animals were used that had any leakage around the catheter.

The animals were fed the weighed amount of food daily at 8:30 a. m. The balloon was emptied daily at 8:30 a. m., 12:30 p. m., 4:30 p. m. and 10 p. m. The secretion was collected for ten or more days after complete healing of the operative wound, and a constant normal was established before cinchophen was given. Cinchophen in doses varying from 0.25 to 2 Gm. daily was then mixed

with the diet, and the same observations were continued. Administration of this drug was continued until the dog died or was killed.

RESULTS

Group 1.—The results obtained from the study of the twelve dogs in group 1 can best be described in a general way as they were identical, or nearly so, in every case. After the subcutaneous injection of histamine, the fasting value for the total gastric acidity, which normally varies from 0 to 40 according to the method of Töpfer, rose to between 100 and 150. This rise usually occurred within the first fifteen minutes, but it always occurred by the end of thirty minutes. There was then a progressive decrease in the value for the total acidity, until at the end of from sixty to ninety minutes the fasting level had been reached.

The volume output of gastric juice fluctuated in direct proportion to the acidity. This output, which varied with the animal, averaged from 100 to 150 cc. during the course of a histamine curve. From 2 to 5 cc. of gastric juice was obtained from the fasting dog. From 30 to 50 cc. was usually obtained at the peak of the acid curve. This amount decreased simultaneously with the acid to the original fasting volume.

A chronic gastric ulcer developed in eleven of the twelve dogs in an average of eighteen days after the administration of cinchophen had been commenced. The twelfth dog received cinchophen for sixty days; at necropsy a grossly normal stomach was found. There was no change at any time in the gastric acidity or volume secretion of gastric juice in this dog.

After the administration of cinchophen, no change was noted in the gastric acidity of the eleven dogs in which ulcers developed. The secretory curve of four of the dogs was prolonged for from thirty to sixty minutes; that is, it required from thirty to sixty minutes more time for the gastric acidity to return to the original fasting level. This occurred after the dog manifested some symptoms of a peptic ulcer and disappeared when the administration of cinchophen was stopped and the ulcer healed.

There was a consistent demonstrable change in the volume output of gastric juice in every case. After the administration of cinchophen, there was no significant change until such symptoms of early gastritis, such as tarry stools and occasional vomiting of small amounts of gastric contents, were present. This change occurred as early as the third day and as late as the twentieth day after the initial dose of the drug had been administered and increased with the development of gastritis. The amount of increased gastric secretion varied from 75 to 200 cc. There was no change in the gross appearance of the gastric contents, such as visible blood, that would account for this increase in the amount of secretion.

When the administration of cinchophen was discontinued there was a gradual decrease of the amount of gastric secretion to the normal level within two weeks. The results obtained with dog A were typical (chart 1). The administration of cinchophen was begun on the eighth day of the study, and on the twentieth day the stools were tarry. Three days later there was marked hypersecretion, which continued. Exploratory laparotomy revealed a gastric ulcer. The administration of the drug was then discontinued and the volume output of gastric juice returned to normal as the ulcer healed.

The symptoms of ulcer were most marked coincident with the largest amount of gastric secretion, and it was at this time that an exploratory laparotomy was generally done. If the administration of cinchophen was continued, the volume output of gastric juice gradually diminished until a definite hyposecretion was present. Within from five to ten days the amount of secretion returned to the normal level or slightly below normal, and after another two weeks it was from 25 to 50 per cent below normal.

This finding is illustrated in part by dog B, which was given 2 Gm. of cinchophen daily. The average normal volume output of gastric juice was 137 cc. A diagnosis of ulcer was made when an average volume of secretion of 257 cc. of gastric juice had been reached. The administration of cinchophen was continued, but there was a gradual decrease in the output of gastric juice, until on the twelfth day of administration there was an average of only 125 cc. The dog was then killed, and a perforating gastric ulcer was found to be present.

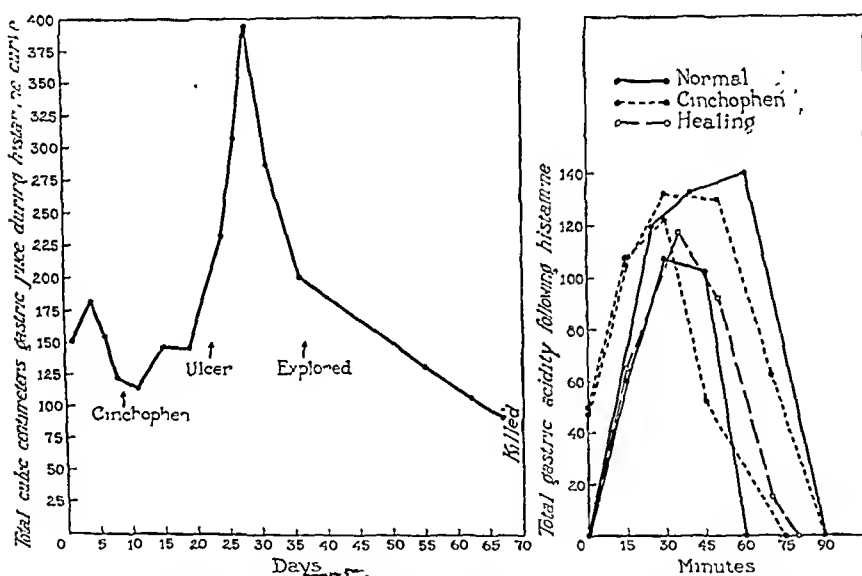


Chart 1.—Total volume output of gastric juice during the different phases of the experiment and total gastric acidity (phenolphthalein indicator) after stimulation with histamine. Daily administration of 2 Gm. of cinchophen was begun on the eighth day and continued to the time of exploration.

Group 2.—The results obtained from observation of the five dogs with fundic pouches confirmed for the most part the results obtained in group 1. The average daily output of gastric juice from the pouches was approximately from 125 to 150 cc. The fasting value for the total gastric acidity varied from 0 to 20. The value for the acidity increased from 8:30 a. m., at which time the dogs were fed, to 12:30 p. m., at which time it varied between 130 and 150, where it remained with only a slight increase until 4:30 p. m. There was then a steady decrease, and at 10 p. m. the average value for the acidity varied from 50 to 75, and by 8 a. m. the fasting level was again reached. The maximal volume output of gastric juice occurred at the time of the greatest acidity, which was at 4:30 p. m.

A peptic ulcer developed in the pouches of all five dogs. When the dose of cinchophen was 1 Gm. or more daily, the ulcers developed in from two to five days and usually perforated. The process was the same as that seen in the intact stomach. In every case the administration of 0.5 Gm. or more of the drug caused evidence of gastritis within eight hours after the initial dose. There was macroscopic evidence of bleeding from the pouches between the fourth and the twelfth hour each day. When a definite ulcer was present this bleeding was so marked in a few cases that the study of the secretion was discontinued. No results have been recorded in which the presence of blood may have been a complicating factor.

The administration of from 0.25 to 2 Gm. of cinchophen daily had no significant effect on the height of the acidity curve. There was, however, the same prolongation of the curve as seen in group 1.

Dog C revealed the typical volume output of gastric juice (chart 2). A normal daily average of 153 cc. was established. One gram of cinchophen was given at

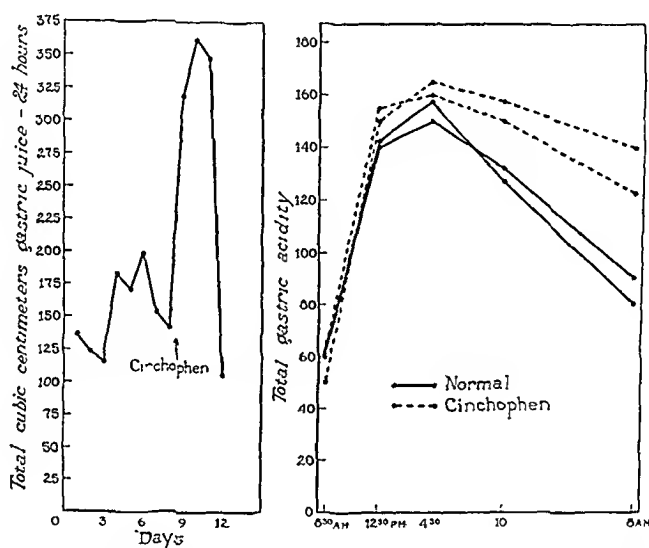


Chart 2.—Total twenty-four hour volume output and the total acidity (phenolphthalein indicator) of the secretion of the fundic pouch of dog C. One gram of cinchophen was administered daily; the dog died of a perforated ulcer of the pouch.

8:30 a. m. At 4:30 p. m. on the same day there was an increase of more than 50 cc. in the volume output. This increase persisted, and the total volume output for the day was 320 cc., or more than twice the amount secreted before the administration of the drug. This hypersecretion continued for seventy-two hours; hyposecretion then developed, and only 100 cc. was secreted. The dog died on the following day as a result of a hemorrhage from a perforated ulcer in the pouch.

Dog D (chart 3) was given 2 Gm. of cinchophen daily. A normal output of 119 cc. of gastric juice per day was established. Eight hours after the initial dose of the drug, the volume output of gastric juice was increased 100 per cent. The total output in twenty-four hours was 203 cc., or nearly 75 per cent more than normal. The following two days the volume output was less than normal. The dog was killed, and a perforated ulcer was found in the pouch.

Dog E was given 0.25 Gm. of cinchophen daily. An average normal output of 209 cc. of gastric juice was established. A definite hypersecretion began during the second twenty-four hours after the administration of cinchophen and persisted for seven days. A maximal output of 323 cc. was reached, and a daily average of 279 cc. was maintained. The dog remained well and had no bleeding during this period.

On the eighth day, 0.5 Gm. of cinchophen was given; bleeding began, and the daily output of gastric juice decreased to 158 cc. One gram of the drug was then given. The bleeding became more marked, and an ulcer developed. Concomitantly, the volume output decreased to from 110 to 122 cc. The dog was killed because of a hemorrhage from the pouch. There were three ulcers, varying from acute to subacute, in the pouch.

The remaining two dogs were given doses of cinchophen varying from 0.5 to 2.5 Gm. The results were similar to those previously described.

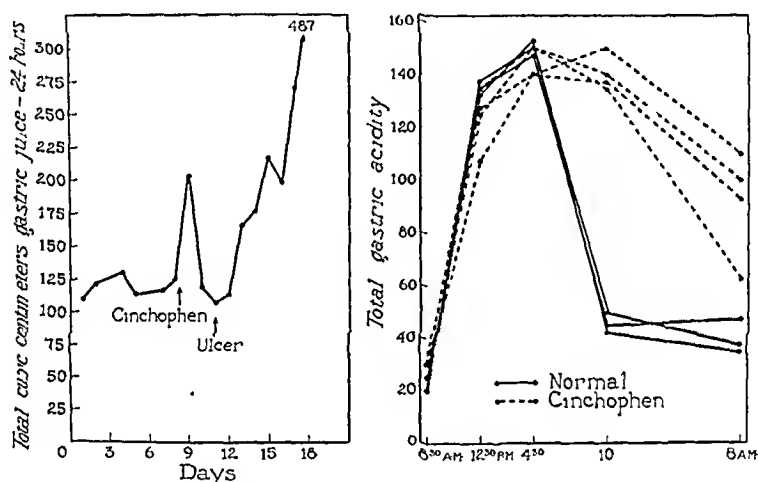


Chart 3.—Total twenty-four hour volume output and the acidity (phenolphthalein indicator) of the secretion of the fundic pouch of dog D. Two grams of cinchophen was administered daily; the increase in the volume of gastric juice after the formation of an ulcer was caused by hemorrhage. Prolongation of the acidity curve may be noted.

COMMENT

These results agree in several respects with the usual findings of the gastric secretion in the presence of gastritis and peptic ulcer in man. The results in group 1 and group 2 nearly parallel each other. With the initial damage of the mucosal cells there is an increase in the amount of gastric secretion, but as more cells are damaged and a definite ulcer occurs, there is a decrease in the amount of secretion. This decrease may be the result of a toxic inhibition of the secreting cells.

In all probability the secretion of the pouches, which was determined, was comparable to the secretion occurring in the stomach proper. The ulcerative process was more rapid in the pouches because of the constant

presence of free acid. A longer study would have been desirable, but the rapidity with which ulcer developed in the isolated gastric pouch and the high incidence of perforation prevented prolonged observations. The amount of bleeding interfered in some cases with the study, but in no case could it be considered a factor in the results.

The ulcer developed during the stage of hypersecretion and was always present at the time of maximal volume output. The increased amount of secretion and consequently a relative increase in the degree of acidity was undoubtedly an important factor in the production of the peptic ulcer from the initial mucosal erosion. The fact that there was no change in the gastric secretion of the one dog in which a peptic ulcer did not develop is at least suggestive.

The action of cinchophen on the gastric secretion is the same as might be expected from a toxin. It is usually accepted that a toxin first stimulates and then depresses. Dog E demonstrates this. When 0.25 Gm. of the drug was given there was a continuous hypersecretion. This dose was not sufficient to produce a peptic ulcer and did not cause any noticeable toxicity. When the toxic dose of 0.5 Gm. was given, a peptic ulcer rapidly developed and there was a marked decrease in the amount of gastric secretion. A further increase in the dose caused a further decrease in the volume of secretion.

SUMMARY

The free and total acidity and the total volume output of the gastric contents were measured during the phases of the development, activity and healing of peptic ulcer which were produced by the administration of cinchophen. A fractional gastric analysis was performed on twelve dogs. The secretion was collected from five fundic pouches at definite intervals throughout the day and night. The results were comparable in the two groups. After the administration of variable doses of cinchophen, there was no change in the level of acidity, but there was an increase in the amount of gastric secretion. This initial hypersecretion was followed by the development of a peptic ulcer and hyposecretion.

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